TOTAL SYNTHESIS OF BREVENAL; SYNTHESIS OF THE AB- AND E- RING SUBUNITS OF BREVENAL AND STUDIES OF OLEFINIC-LACTONE RING-CLOSING METATHESIS USING A REDUCED TITANIUM ALKYLIDENE; SYNTHESIS OF (*R*)-(-)-MUSCONE AND (*R*)-(+)-MUSCOPYRIDINE

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

This dissertation describes the total synthesis of the marine ladder toxin brevenal utilizing a convergent synthetic strategy. Critical to the success of this work was the use of olefinic-ester cyclization reactions and the utilization of glycal epoxides as precursors to C-C and C-H bonds. Previous total syntheses of brevenal and our strategy for the completion of the molecule are discussed in detail.

In addition, olefinic-lactone cyclization reactions that result in the generation of macrocycles are described. The methodology was used to synthesize the natural products muscone and muscopyridine.

Dedicated to the memory of my friend and colleague:

Christopher William Nielsen

1977 ~ 2008

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STANDARD LIST OF ABBREVIATIONS

$[\alpha]_D^{20}$	specific rotation, expressed as a unitless number units, $°cm^2/g$
Å	Ångström
Ac	acetyl
AcOH	acetic acid
$AlMe_3$	trimethyl aluminum
$BF_3•OEt_2$	boron trifluoride etherate
BH_3•DMS	borane dimethylsulfide complex
Bn	benzyl
BPS	*tert*-butyldiphenylsilyl
n-Bu	butyl
t-Bu	*tert*-butyl
n-BuLi	*n*-butyllithium
Bu_2BOTf	dibutylboron triflate
Bz	benzoyl
°C	degrees Celsius
calcd	calculated
$CDCl_3$	deuterated chloroform
$CHCl_3$	chloroform
CH_2Cl_2	dichloromethane

CI	chemical ionization
COSY	correlation spectroscopy
*m*CPBA	*m*-chloroperoxybenzoic acid
CSA	camphorsulfonic acid
d	day(s); doublet (spectral)
DCC	1,3-dicyclohexylcarbodiimide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene,
DDQ	2,3-dicyano-5,6-dichloro-parabenzoquinone
dr	diastereomeric ratio
DEPT	distortionless enhancement by polarization transfer
DIBAL	diisobutylaluminun hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMS	dimethylsulfide
DMSO	dimethyl sulfoxide
EI	electron ionization
er	enantiomeric ratio
Et	ethyl
EtOH	ethanol
Et_2O	diethylether
EtOAc	ethyl acetate
EI	electron impact
Et_3N	triethylamine
g	gram(s)

GC	gas chromatography
h	hour(s)
HMDS	hexamethyldisilazane
HRMS	high-resolution mass spectrum
Hz	hertz
IC_{50}	50% inhibitory concentration
iPr_2NH	diisoproylamine
IR	infrared
J	coupling constant (in NMR)
KH	potassium hydride
LAH	lithium aluminum hydride
LDA	lithium diisopropyl amide
LiHMDS	lithium hexamethyldisilazide
LRMS	low-resolution mass spectrum
M	molarity, mol/L; mega
Me	methyl
MeCN	acetonitrile
MeLi	methyl lithium
MeOH	methanol
$MgSO_4$	magnesium sulfate
MHz	megahertz
min	minute(s)
mL	milliliter
mol	mole(s)
mp	melting point

MS	mass spectrometry; molecular sieves
M/Z	mass to charge ratio (in mass spectrometry)
NaBH4	sodium borohydride
NaH	sodium hydride
NaHMDS	sodium hexamethyldisilazide
$NaHCO_3$	sodium bicarbonate
$NaHSO_4$	sodiumhydrogen sulfate
Na_2SO_4	sodium sulfate
NH_4Cl	ammonium chloride
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
OsO_4	osmium(IV) oxide
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	*para*-methoxybenzyl
$P(OEt)_3$	triethylphosphite
ppm	parts per million (in NMR)
PPTs	pyridinium *p*-toluenesulfonate
*i*Pr	isopropyl
$(iPr)_2NH$	diisopropylamine
py	pyridine
q	quartet (spectral)

quant	quantitative
R_f	retention factor (in chromatography)
RCM	Ring-Closing Metathesis
rt	room temperature
s	singlet (spectral); second(s)
SO_3 •py	sulfur trioxide pyridine complex
t	triplet (spectral)
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*tert*-butyldimethylsilyl
TES	trimethylsilyl
Tf	trifluoromethanesulfonoyl, triflate
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl, tetramethylsilane
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPAP	tetrapropylammonium perruthenate
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic

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I owe my deepest gratitude to my advisor, Professor Jon D. Rainier, who has played a pivotal role in my education and life. Professor Rainier has continually challenged and inspired me, which not only has aided in my development as a scientist but also enhanced my character. None of the work presented herein would have been possible without his guidance and support.

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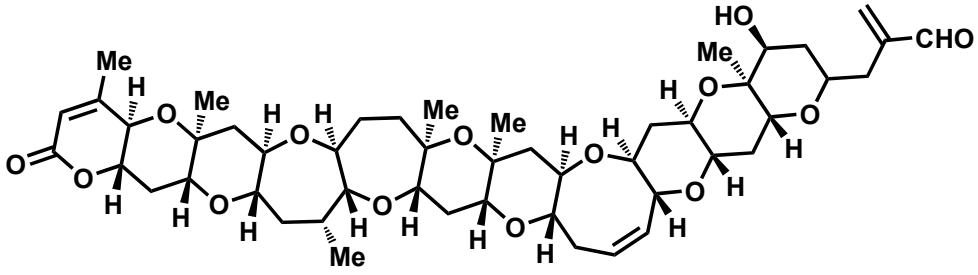
CHAPTER 1

THE TOTAL SYNTHESIS OF BREVENAL; SYNTHESIS OF THE AB- AND E- RING FRAGMENTS

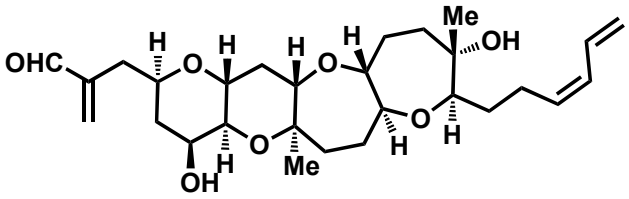
Introduction

The term "red tide" refers to a phenomenon where harmful algae known as dinoflagellates accumulate rapidly along costal regions and results in the discoloration of surface water. The dinoflagellates have a dramatic effect on the life around them during the warm months of the summer when they "bloom" or reproduce.[1] The species reproduce in such great numbers the water may appear red thus producing a "red tide". These events are relatively common along the coast of Florida and are responsible for massive fish kills, neurotoxic shellfish poisoning and other human health problems.[2] The potency of the red tide is governed by the concentrations of the marine dinoflagellates that produce a range of highly potent polycyclic ether toxins.[1,2]

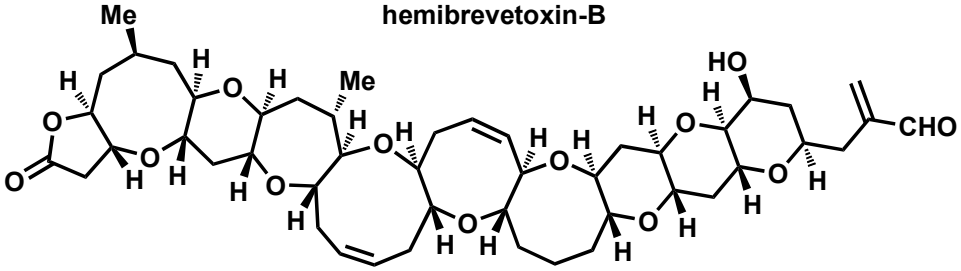
Among this array exist a structurally unique class of molecules called the brevetoxins that are produced by the dinoflagellate *Karenia Brevis* (Figure 1.1). Although unrelated to the red tide events, the ciguatoxins are a structurally similar class of molecules that are produced by the dinoflagellate *Gambierdisicus Toxicus* (Figure 1.2). The brevetoxins are associated with nuerotoxic shellfish poisoning (NSP) while the



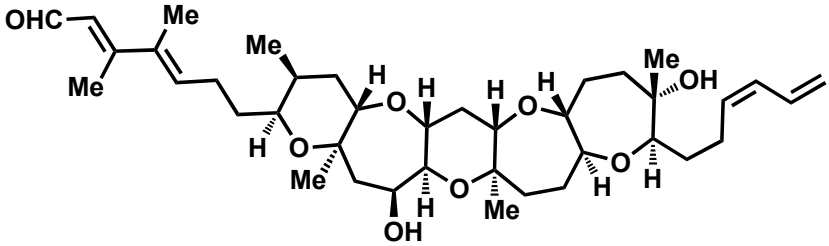
brevetoxin-B



hemibrevetoxin-B



brevetoxin-A



brevenal

Figure 1.1. Representative examples of polycyclic ether natural products

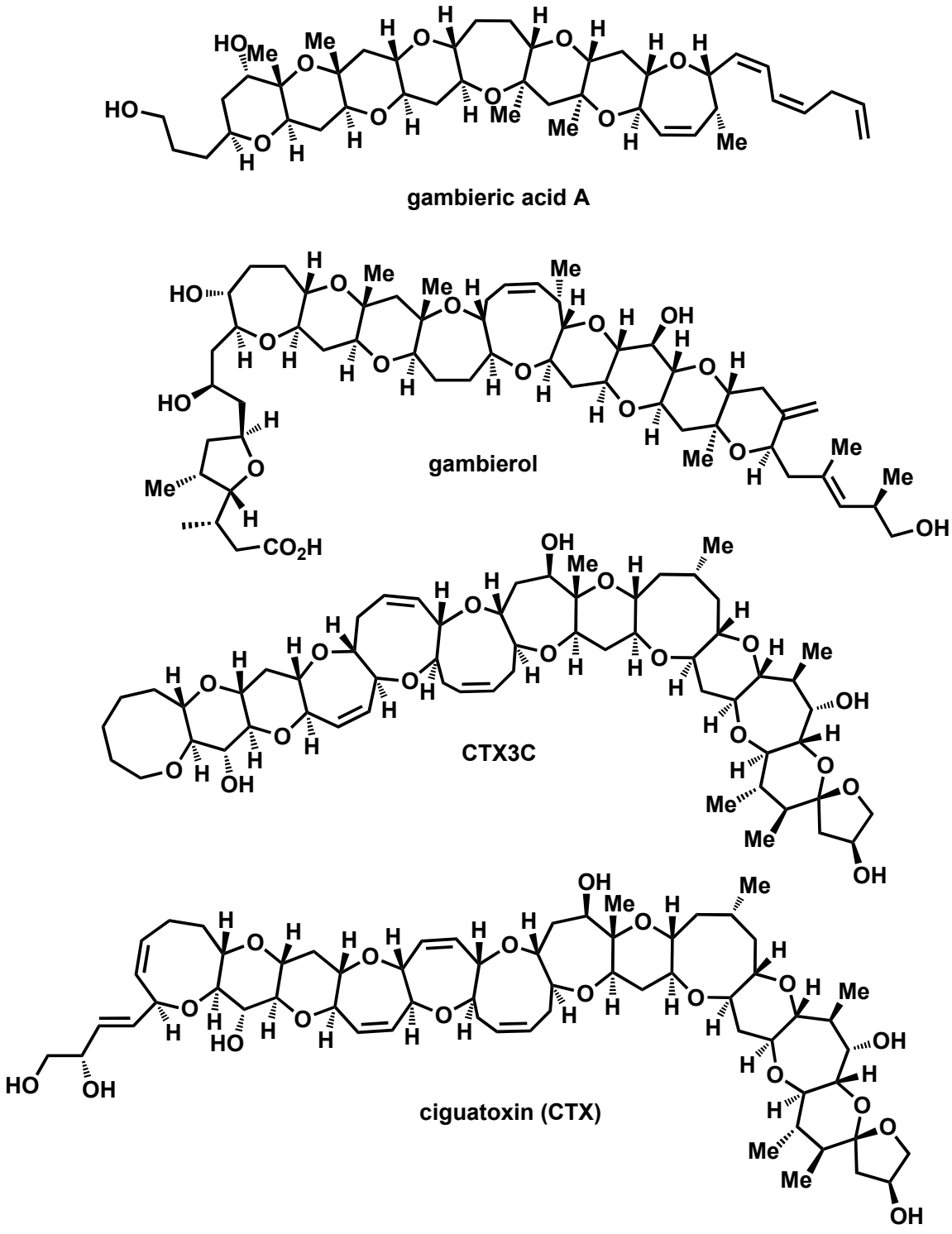


Figure 1.2. Representative examples of polycyclic ether natural products

ciguatoxins are associated with ciguatera poisoning.[3-5] The environmental and human health effects associated with the two classes of molecules have attracted a great deal of attention from the scientific community. Unique to the blooms of *Karenia Brevis* is the associated aerosolized toxin component.[6-8] Inhalation of the airborne brevetoxins causes respiratory distress to humans and other mammals along the shore of the red tide phenomena. Also, when humans consume shellfish contaminated with the brevetoxins mild to severe gastrointestinal and neurological symptoms may occur.[9,5]

Much like the brevetoxins, the ciguatoxins display their poisoning effects through the same food chain cycle. Human consumption of infected marine animals causes "ciguatera poisoning" whose diagnosis relies on symptoms of muscle pain, diarrhea, vomiting and sensory disorders.[3,4] These symptoms can last from weeks to years, and in extreme cases for as long as 20 years.[10,11]

Despite the efforts the scientific community has put forth to understanding the biological properties of these molecules, there is no drug on the market to treat these illnesses. Perhaps the last place one may expect to find a drug candidate would be from the harmful algae blooms produced from *K. Brevis*. Yet, brevenal, a compound that has been shown to inhibit the binding of brevetoxins was found to be produced by *K. Brevis*. Brevenal represents one of the newest members of the brevetoxin family and was isolated from laboratory cultures of *K. Brevis* by Baden and coworkers.[12-14] Brevenal's structure closely resembles that of hemibrevetoxin B, isolated by Shimizu and coworkers in 1990, having a pentacyclic *trans*-fused polyether scaffold.[15] Brevenal's unique antagonistic properties were serendipitously discovered when A. Bourdelais prevented the death of guppies that were exposed to brevetoxin by treating them with a dilute sample of

brevenal.[12,14] This result implies that brevenal acts as an antagonist towards brevetoxin. It has been shown that the brevetoxins and ciguatoxins exhibit their neurotoxicity by binding to the receptor site 5 of voltage-gated sodium channels (VGSC).[16-19] VGSC's are membrane proteins that allow sodium ions to pass through a cell's plasma membrane. The breveotoxins are thought to orient in a "head down" orientation into the VGSC as shown in Figure 1.3.[20] When brevetoxins bind to the VGSC the channels open at normal resting potential with an increase in mean channel open time. This in turn causes a persistent depolarization of the cell and ultimately leads to apoptosis through inhibition of channel inactivation.[21-23]

Lepage and co-workers were able to show that brevenal competitively displaces brevetoxin from site 5 on VGSC in rat brain synaptosome receptors in a concentration dependant manner with a K_i value of 1.85 μM.[24] These results suggest that brevenal may be used to treat humans and marine organisms that have been exposed to brevetoxins.

In another study, Abraham and co-workers studied the airway responses to inhaled brevetoxins and brevenal in a sheep asthma model that share many characteristics of the disease in humans. The inhalation of brevetoxins induce pathophysiologic effects such as bronchoconstriction and a decrease in tracheal mucous velocity.[25] They were also able to show for the first time *in vivo* that brevenal is able to inhibit the brevetoxin-induced bronchoconstriction.

Abraham found that brevenal provides the same increase in tracheal mucous velocity at one-million fold lower concentrations as seen with amiloride, a leading drug to improve mucociliary clearance in cystic fibrosis patients.[25,26] Thus, brevenal, in addition to its potential thearupeutic abilities in the treatment of NSP, shows promise for

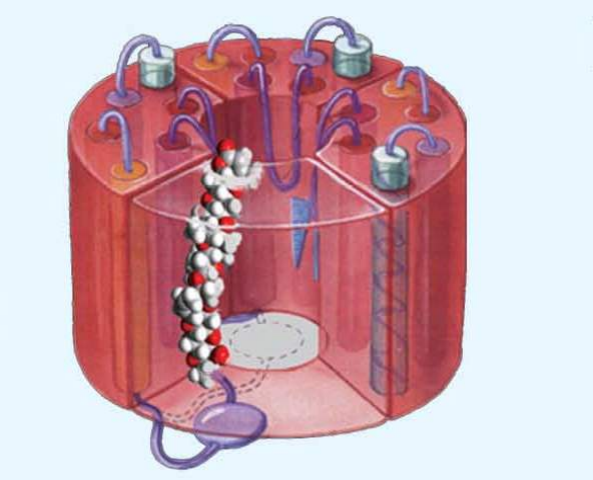


Figure 1.3. Illustration of brevetoxin binding to site 5 of a VGSC

the treatment of diseases associated with mucociliary dysfunction.

Previous Syntheses

A common feature of marine polycyclic ether natural products is a "ladder-shape" *trans* fused polyether skeleton composed of five to nine membered cyclic ether rings. The diverse molecular framework of polycyclic natural products that nature has produced has prompted equally diverse strategies to synthesize these molecules. Our group has developed a very flexible and iterative strategy to assemble the framework of polycyclic ether natural products, such as brevenal.[27] However, before divulging our work, the previous synthesies of brevenal warrant discussion. From a chronological perspective, Sasaki's synthesis of brevenal will be discussed first followed by work from Yamamoto and the Crimmins laboratories.

Sasaki's synthesis

Sasaki and coworkers were the first to synthesize brevenal in 2006.[28] Sasaki's work led to a revision of the originally proposed structure of brevenal (Figure 1.4). On the basis of NMR distinctions between synthetic and natural brevenal, a revised structure differing only in the configuration of the C26 teriatary alcohol had been proposed and later confirmed by Sasaki's total synthesis of brevenal.[29] The revised structure **1.1** is also consistent with the biosynthetic pathway for polycyclic ether marine natural products proposed independently by Shimizu and Nakanishi.[30-35] It is believed that nature constructs polycyclic ether natural products through a polyepoxide cyclization cascade as shown in Figure 1.5. From the poly-ene **1.3**, a series of enzymatically-mediated

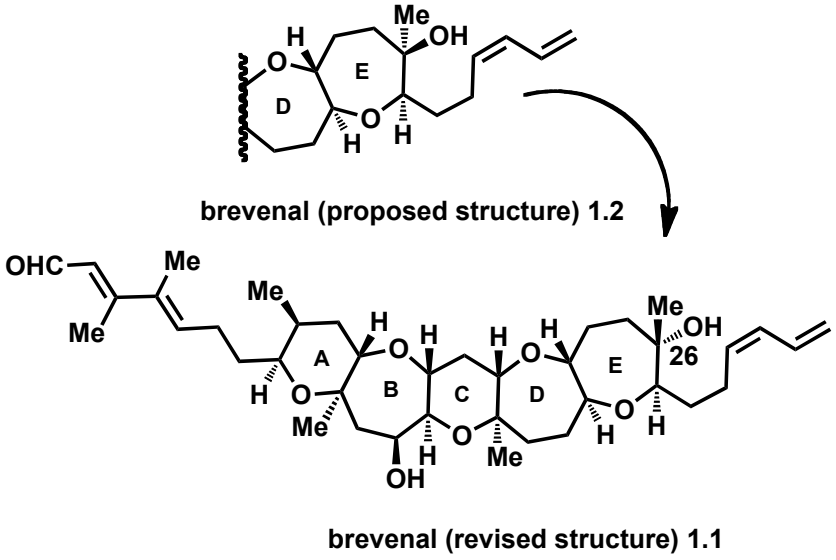


Figure 1.4. Structural revision of brevenal.

epoxidations occur to generate poly-epoxide **1.4**. Ring opening at the more substituted carbon with a molecule of water occurs with inversion of the epoxide stereochemistry thereby setting the C26 stereochemistry.

Sasaki's retrosynthetic plan is shown in Figure 1.6.[29] Sasaki planned for the late stage introduction of both unsaturated side chains: The left hand side chain, containing a sensitive (*E*,*E*) diene moiety, was to be constructed using a Stille coupling between vinyl iodide **1.5** and vinyl stannane **1.6**; and the right-hand-side chain was to be constructed from Wittig salt **1.7**. The pentacyclic core was to be convergently synthesized through the coupling of AB ring enol phosphate **1.8** and the DE ring exocyclic enol ether **1.9** using a Suzuki-Miyaura coupling.

The synthesis of the AB ring subunit commenced with Evan's *syn*-aldol adduct **1.10** prepared on gram scale (Figure 1.7) in order to meet the demands of material throughput.[36] Treatment of the nitrile with DIBALH as the reducing agent gave the corresponding aldehyde. The aldehyde was then treated with a Wittig reagent to give the unsaturated ester **1.11** in 97% yield. Reduction of the ester with DIBALH gave the allylic alcohol. Sharpless asymmetric epoxidation of the resultant allylic alcohol **1.12** gave epoxide **1.13** as a single stereoisomer in 88% yield. The alcohol was oxidized to the aldehyde whereupon Wittig olefination provided the vinyl epoxide **1.14**. In a single flask, Sasaki achieved oxidative cleavage of the PMB ether along with 6-*endo* ring closure forming the A ring **1.15**.[37] The free secondary alcohol was protected as

a TES ether and hydroboration of the vinyl group with disiamylborane gave **1.16**. Another oxidation/Wittig olefination reaction yielded the unsaturated ester **1.17**. The cyclic lactone **1.18** was formed from **1.17** via TES ether cleavage, hydrogenation

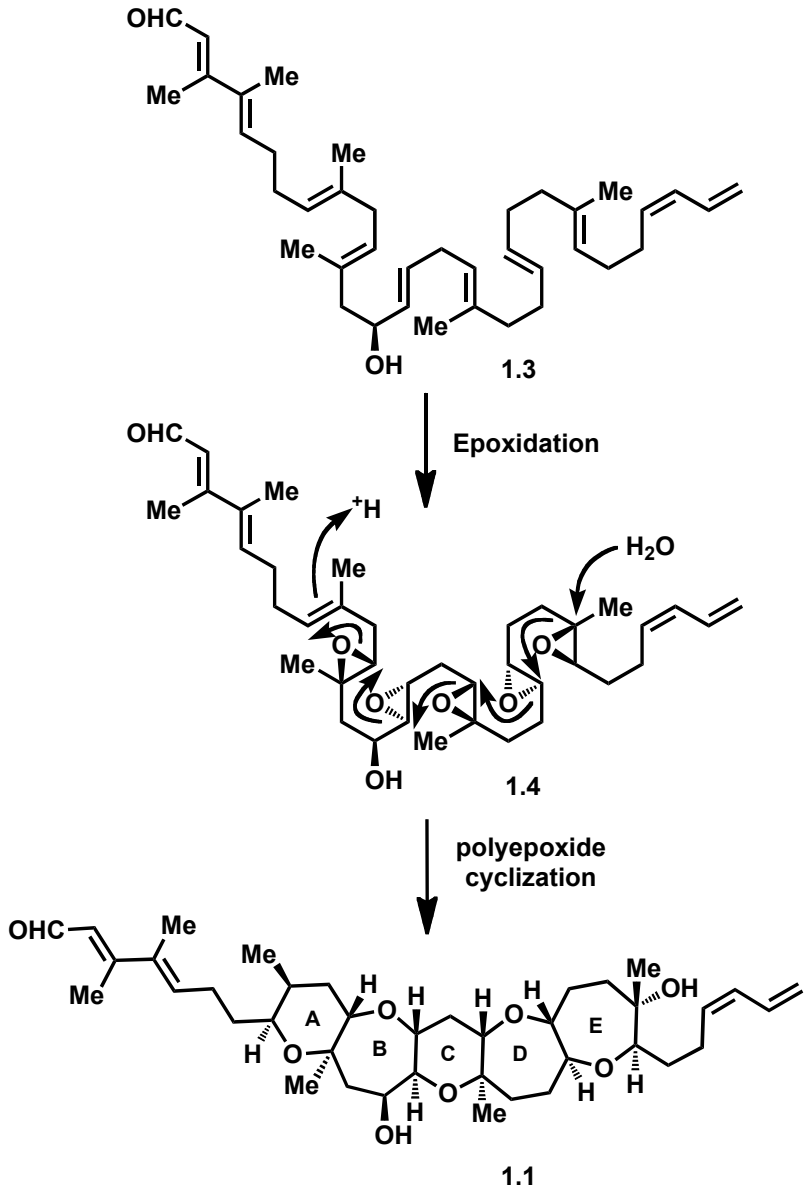


Figure 1.5. Proposed biomemetic synthesis of brevenal

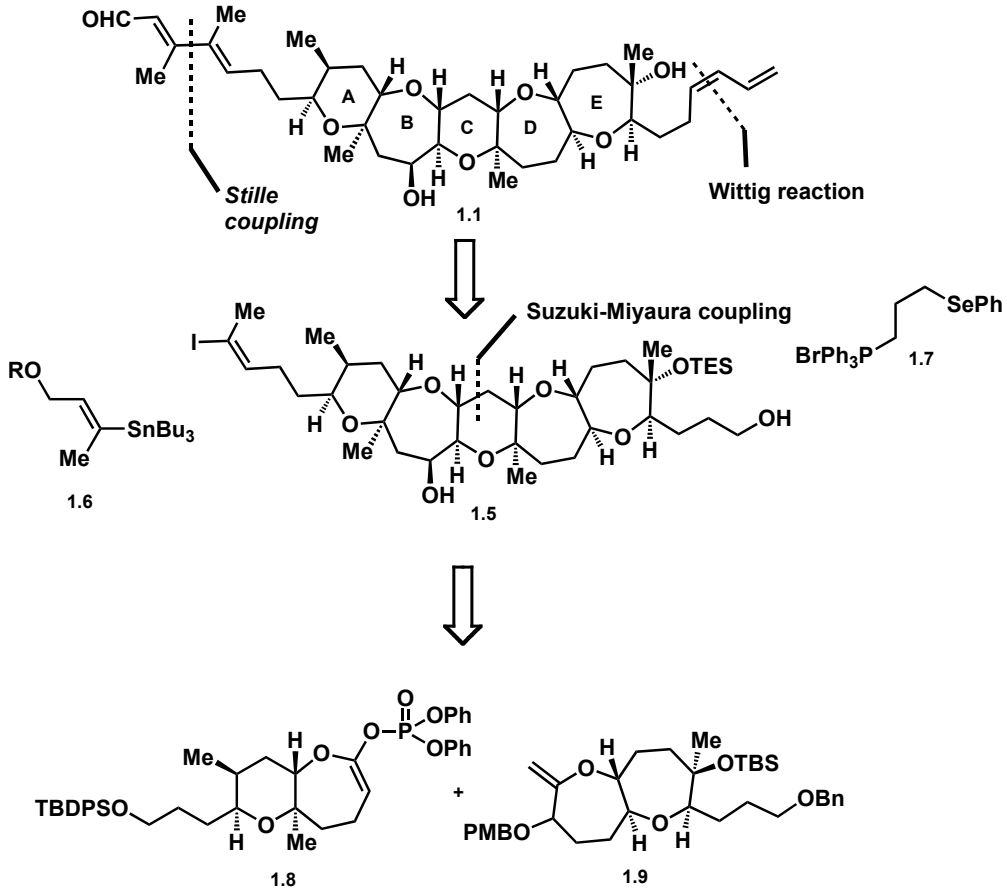


Figure 1.6. Sasaki's retrosynthetic analysis

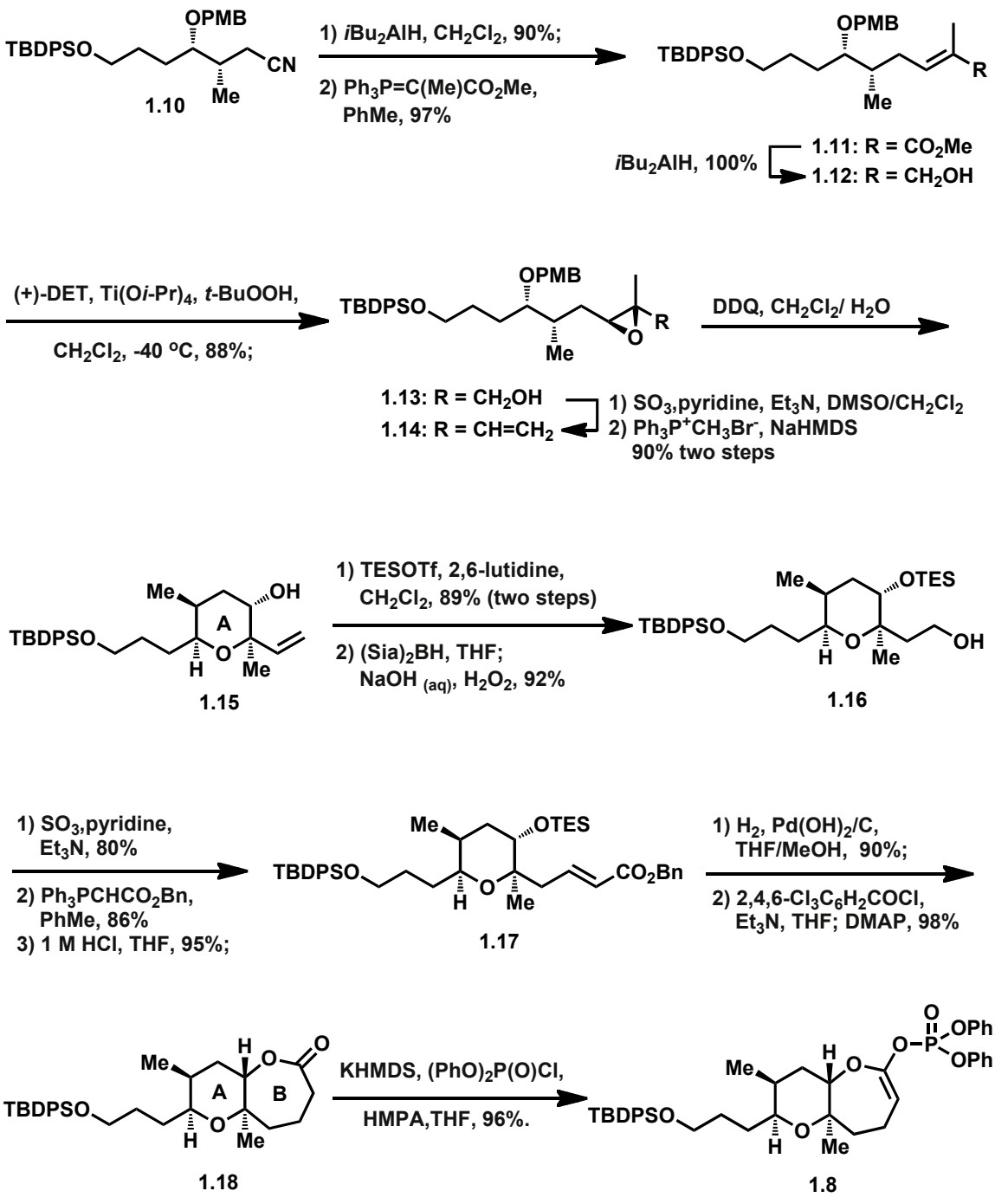


Figure 1.7. Synthesis of the A ring.

followed by lactonization using Yamaguchi's protocol.[38] Transformation of **1.8** to the requisite AB ring enol phosphate **1.18** was accomplished by treatment of **1.18** with the phosphorous oxychloride and base.

Sasaki's stereoselective synthesis of the DE ring fragment (Figure 1.8) is reminiscent of Kadota and coworkers' synthesis of the H ring of Gamberiol.[39] They planned the construction of the seven-membered cyclic ether using an intramolecular reaction of an allylstannane with an aldehyde. They commenced the synthesis with benzylidene ester **1.19** that was prepared from 2-deoxy-D-ribose in three steps by a known procedure.[40] The α,β−unsaturated ester was treated with ozone followed by a Wittig reaction to give olefin **1.20** in 80% yield.

Hydroboration of **1.20** with 9-BBN afforded the primary alcohol in 94% yield. Protecting group manipulations were then made to deprotect the secondary alcohol and selectively protect the primary alcohol as a TBS ether to give **1.21**. The cyclization precursor **1.22** was then prepared through an allylation/stannylation procedure followed by oxidation to give the aldehyde **1.23**. Sasaki was able to generate the oxepene **1.24** in excellent yield by treatment of **1.23** with BF_3-OEt_2.

With the D ring in hand, Sasaki set out to append the E ring using a samarium diiodide mediated reductive cyclization (Figure 1.9). Accessing the cyclization precursor required oxidation state and protecting group manipulation. Thus, benzylation then ozonolysis of **1.24** accompanied by a reductive workup afforded the alcohol which was protected as the benzyl ether to give **1.25**. The acetal was then removed under acidic conditions giving diol **1.26** quantitatively. A single flask triflation/TBS protection sequence was carried out yielding the primary triflate that was then directly subjected to

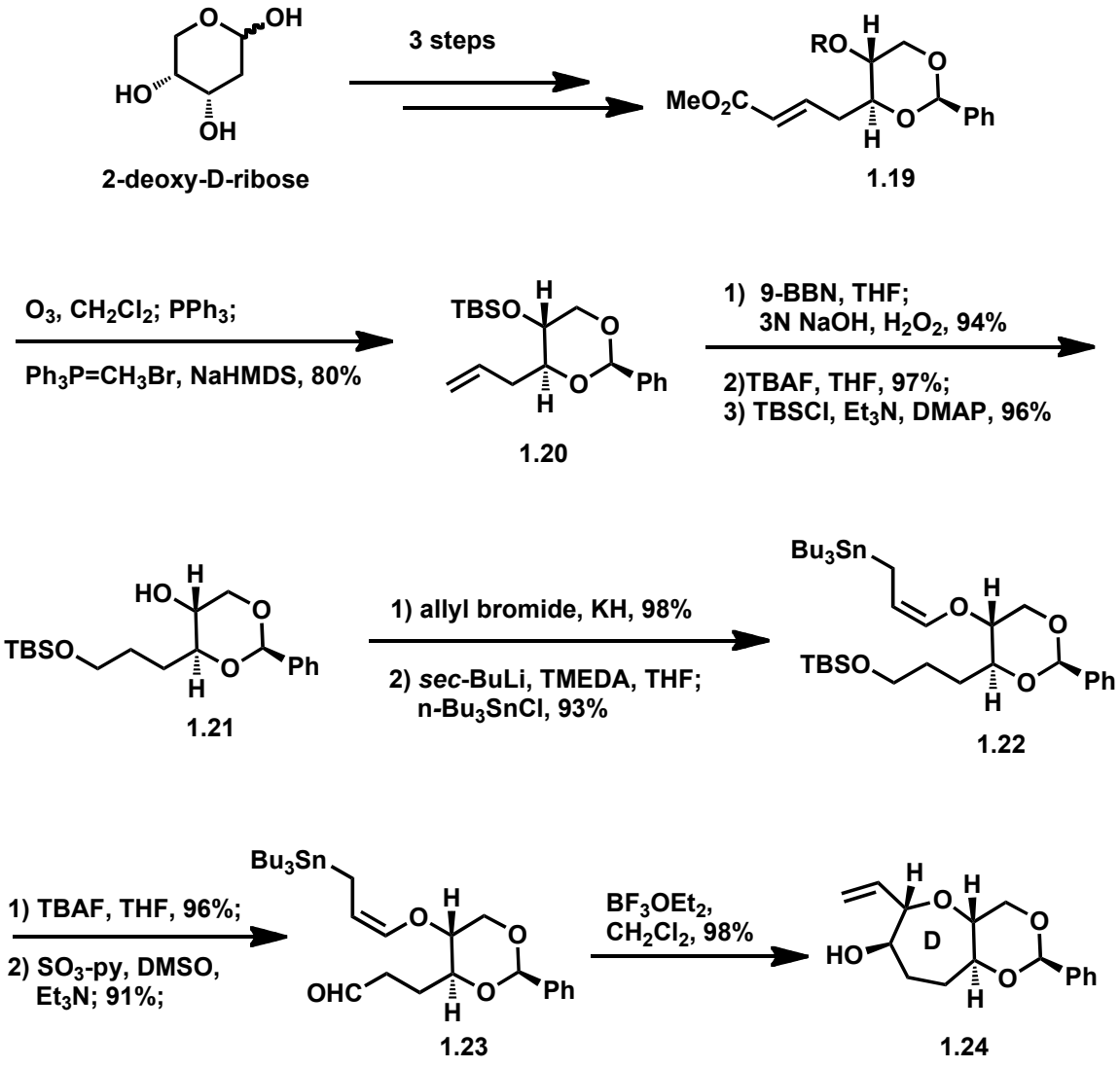


Figure 1.8. Construction of the D Ring

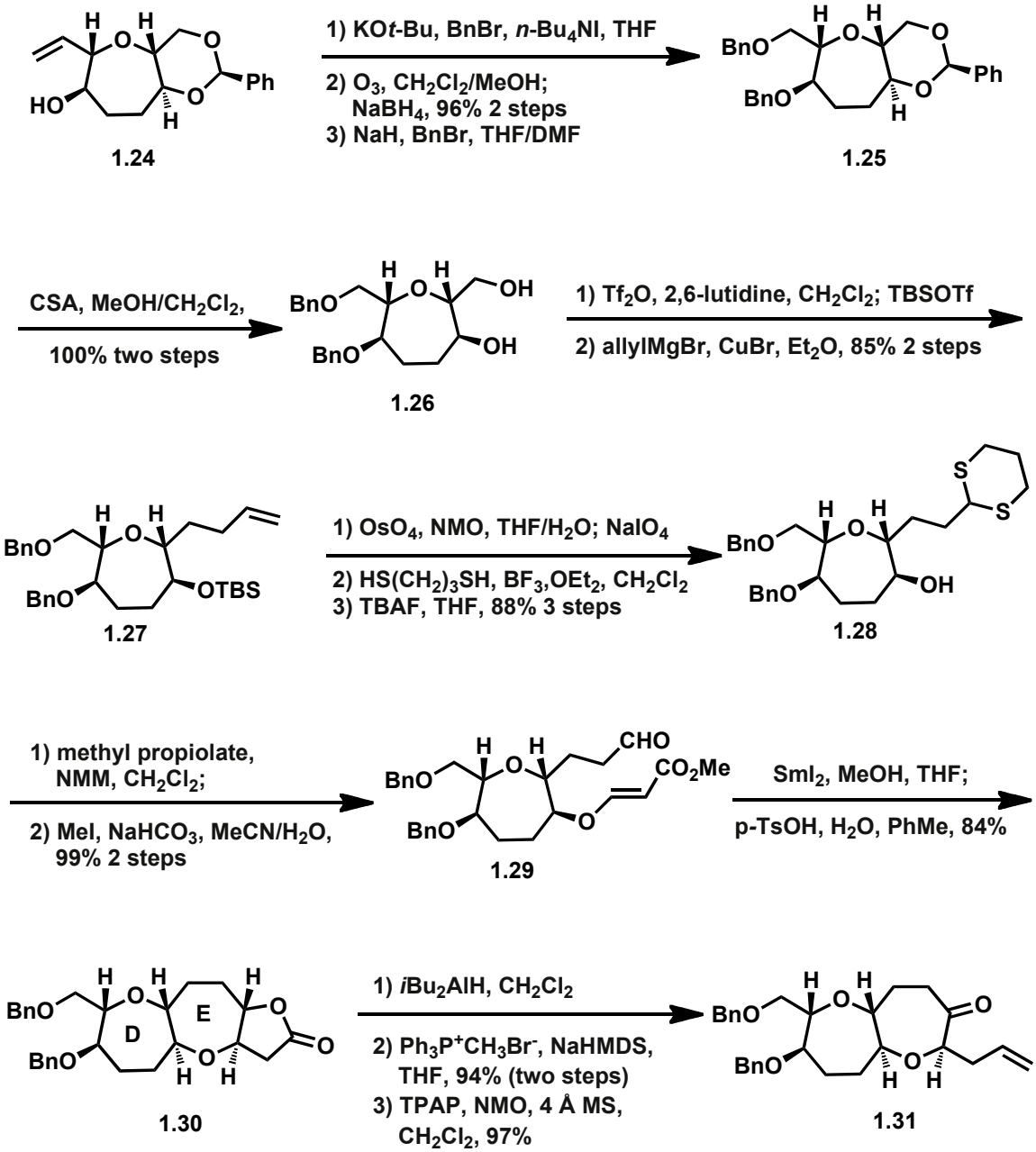
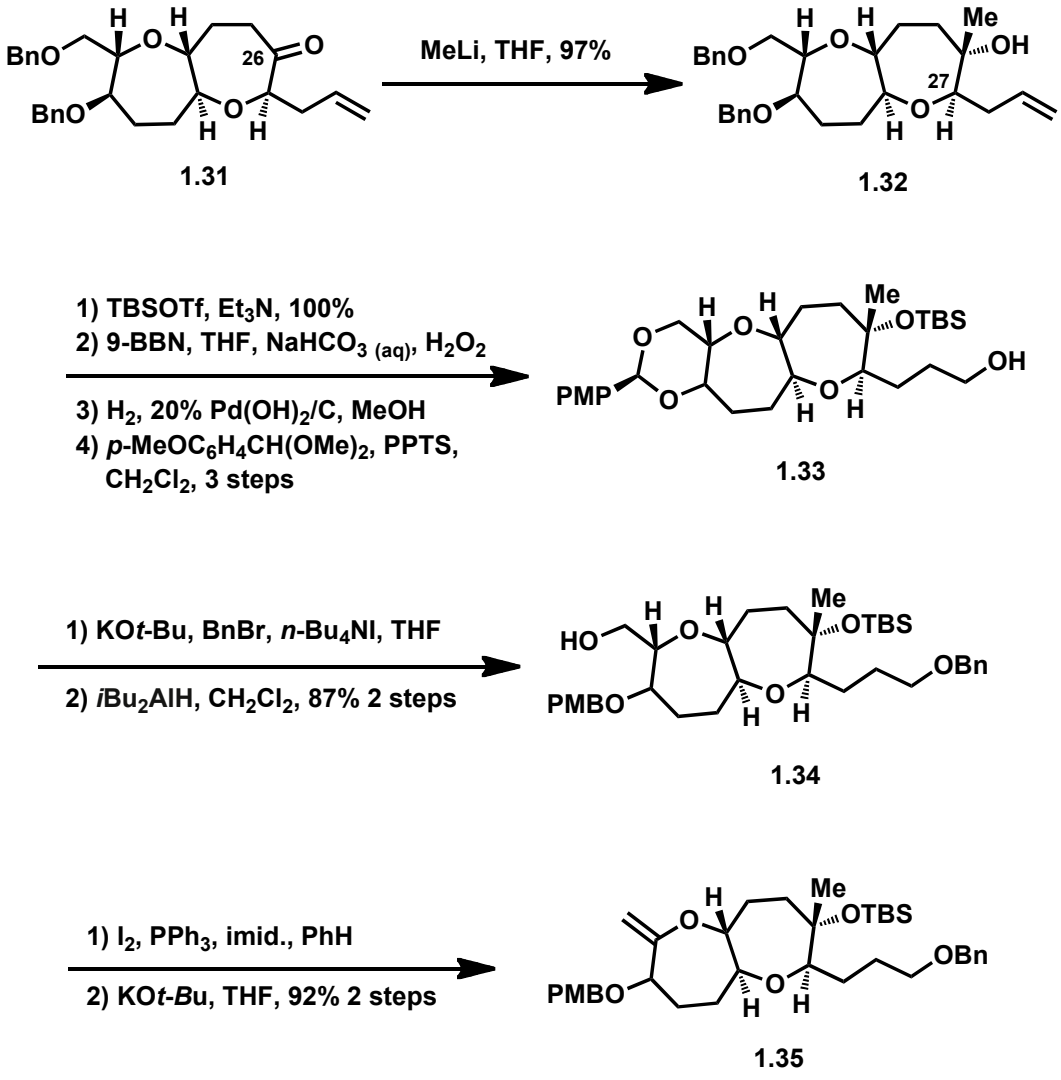


Figure 1.9. Construction of the E Ring

reaction with allyl cuprate giving the homologated product **1.27**.[41] Oxidative cleavage of the terminal olefin provided the aldehyde, which was protected as the dithiane. The silyl ether was cleaved and the resultant free alcohol **1.28** was subjected to hetero-Michael conditions using methyl propiolate as the Michael acceptor. The aldehyde was then unmasked to give the reductive cyclization precursor **1.29**. Exposure of **1.29** to SmI_2 followed by acidic workup provided **1.30** as a single stereoisomer.[42] Next, half reduction of the lactone using *i*Bu_2AlH at low temperatures was followed by Wittig reaction giving a terminal olefin. The secondary alcohol was oxidized to the ketone **1.31** using TPAP and NMO.[43]

Sasaki next targeted the C26 stereocenter. Different methyl nucleophiles were investigated and it was found that addition of methyllithium in THF at -78 °C provided a 10:1 mixture of diastereomers favoring the desired product **1.32** (Figure 1.10). Sasaki confirmed the addition had provided the correct stereochemistry at C26 through an nOe correlations.[29] The same NOE correlation was not observed for the undesired diasteromer.

The tertiary alcohol **1.32** was protected as a TBS ether and the terminal olefin was then subjected to a hydroboration and oxidation sequence. The benzyl groups were reductively removed and the secondary alcohol was ultimately protected as the PMB ether **1.34** through a benzylidene acetal formation/*i*Bu_2AlH reduction sequence. The exocyclic olefin was produced through an iodination and subsequent base promoted elimination to afford the DE ring coupling subunit **1.35**. After Sasaki had finished the synthesis of both of the coupling subunits, he turned his attention to their coupling and the completion of brevenal's pentacyclic core as shown in Figure 1.11. The coupling of the two subunits was achieved by using a Suzuki coupling reaction.



1.31 1.32 1.33 1.34 1.35

Figure 1.10. Introduction of the C26 stereocenter and completion of the coupling subunit

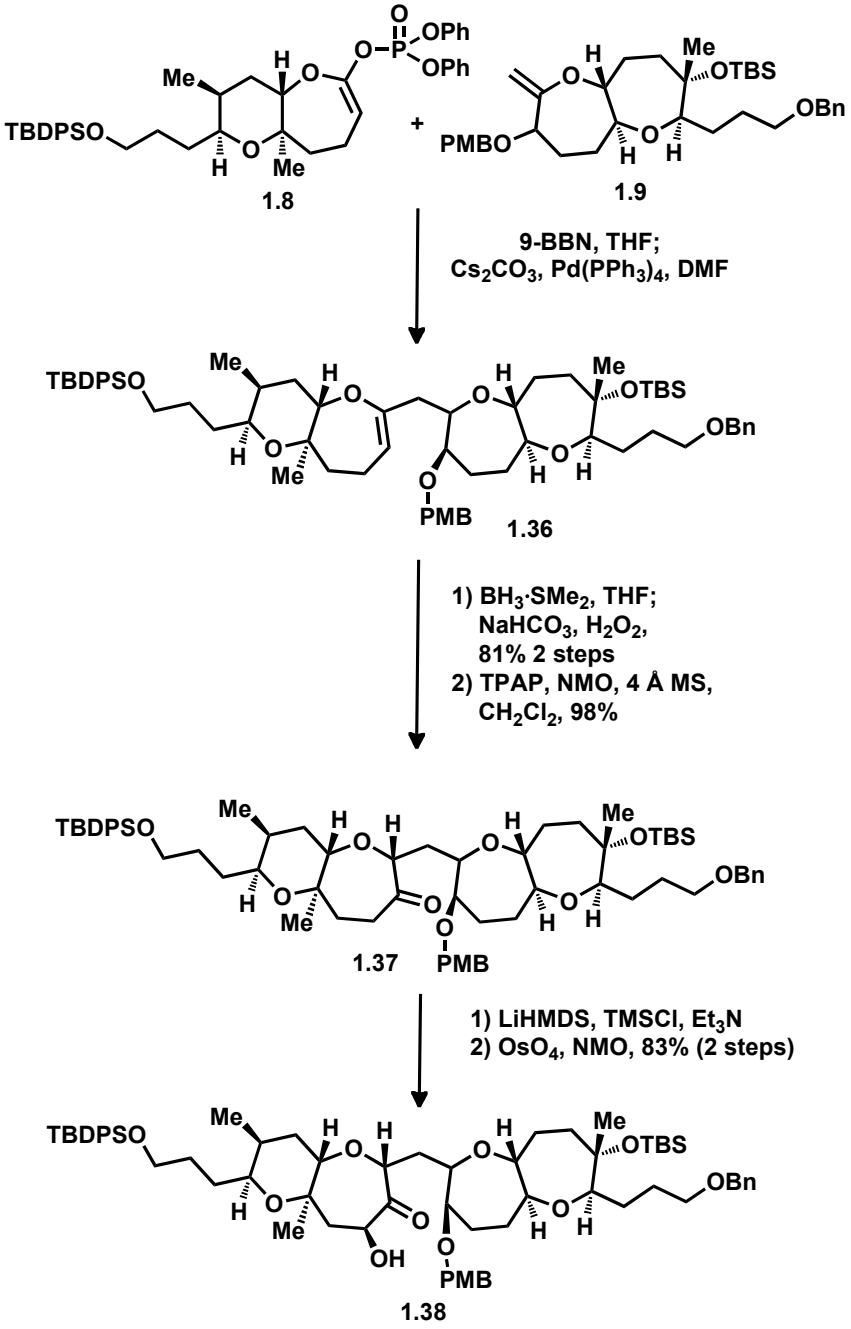


Figure 1.11. Suzuki-Muyaira coupling of enol phosphonate **1.8** and enol ether **1.9**

The requisite borane was generated from the DE ring exocyclic enol ether by treatment with 9-BBN. This was directly subjected to reaction with enol phosphate **1.8** under Suzuki conditions. The coupling product was isolated as a single stereoisomer. The ketone within **1.37** was installed through a hydroboration/oxidation sequence from enol ether **1.36**. Oxidation of the enolate using OsO_4 provided the α–hydroxyketone **1.38** in good yield.[44] Reduction of **1.38** with iBu$_2$AlH proceeded with good diasteroselectivity (10:1) to give the diol **1.39** (Figure 1.12). The diol **1.39** was bis-TES protected and the PMB ether was oxidatively cleaved providing a secondary alcohol, which was oxidized to the ketone **1.40** via TPAP and NMO conditions.[43] To complete the core, the angular C19 methyl needed to be installed. This was done via formation of a mixed thioketal from the corresponding ketone **1.40**. In a single flask, the thioketal was oxidized with *m*CPBA to the sulfone and then displaced with $AlMe_3$ thereby setting the C19 angular methyl.[45-47] The C14 alcohol was reprotected with TBSOTf to provide the pentacyclic polyether core of brevenal **1.41**. In an additional eight steps intermediate **1.42** was obtained.

At this point, all that was left to complete the total synthesis of brevenal was: 1) introduction of the left (*E*,*E*)-dienal side chain; 2) introduction of the right-hand diene side chain; 3) global deprotection, and; 4) chemoselective oxidation. The installation of the (*E*,*E*)-dienal side chain was envisioned to utilize a Stille coupling. To do this, vinyl iodide **1.43** was regioselectivly synthesized from alkyne **1.42** through silylcupration using $(Me_2PhSi)_2Cu(CN)Li_2$ followed by its treatment with NIS (Figure 1.13)[48,49] Vinyl iodide **1.43** was formed as a 9:1 mixture of regioisomers (Figure 1.13). After extensive model studies, optimal Stille coupling conditions were found when using $Pd_2(dba)_3$/Ph_3As/CuTC

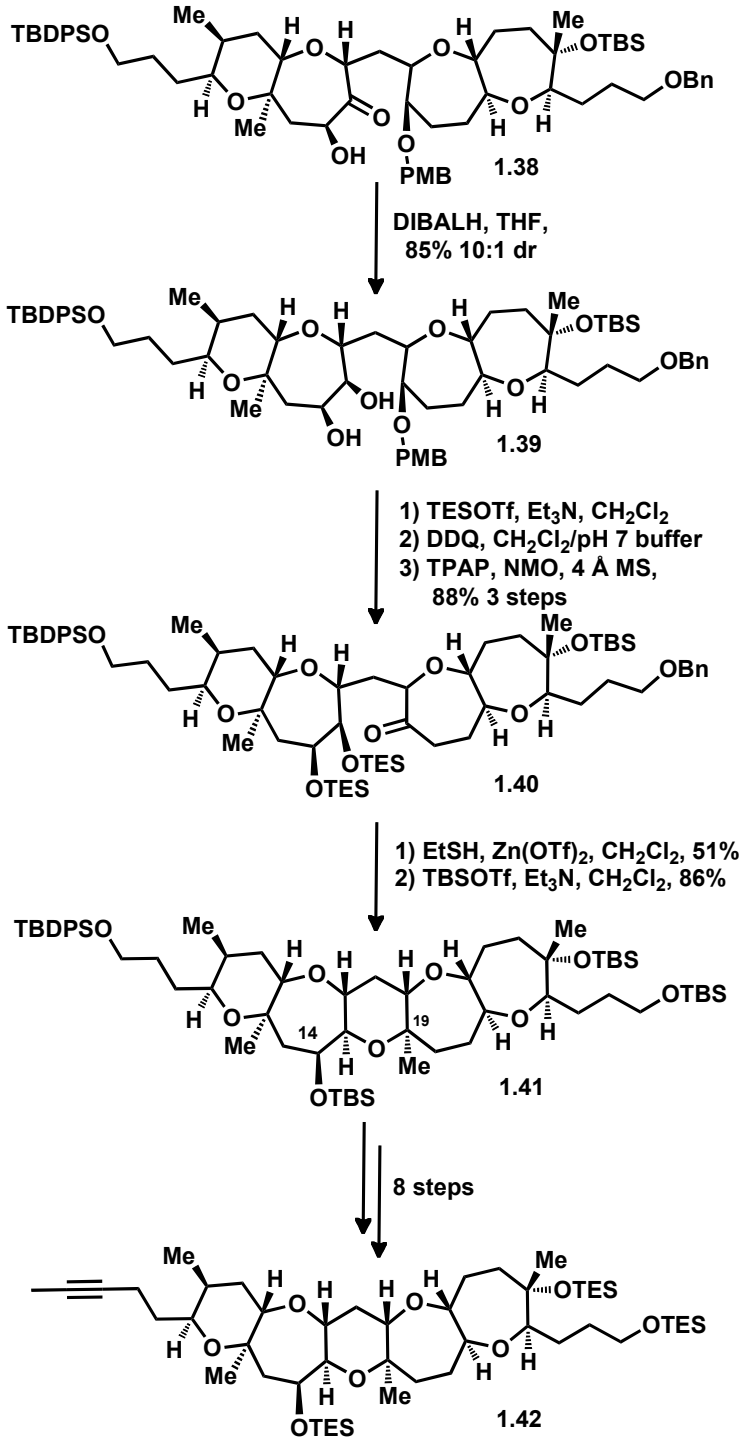


Figure 1.12. Installation of the C19 angular methyl and completion of the core

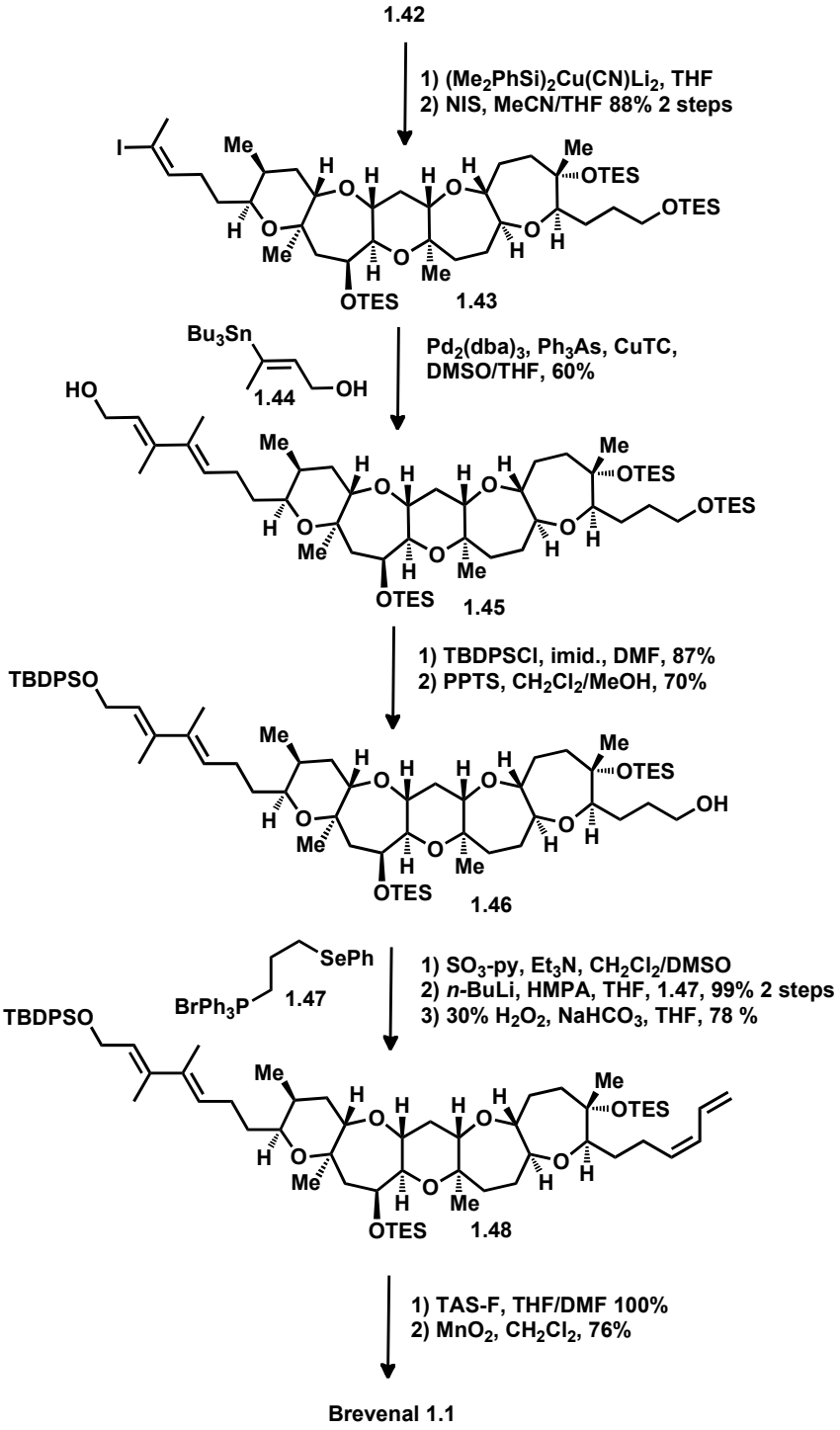


Figure 1.13. Installation of the side chains and completion of the synthesis

as the catalyst system to provide **1.45** in 60% yield.[50] The allylic alcohol was protected with TBDPSCl and the primary TES ether was cleaved with PPTS/MeOH to give **1.46**. The right-hand (*Z*)-diene side chain was introduced using the procedure developed by Nicolaou et al. that consists of oxidation of the primary alcohol **1.46** to the aldehyde followed by Wittig olefination using ylide **1.47** and subsequent elimination of the selenide to give **1.48** in good yield.[51,52] Finally, global deprotection and chemoselective oxidation of the C1 alcohol provided the dienal and completed the total synthesis of brevenal. Sasaki makes note that the synthetic brevenal exhibited identical spectral behavior to that of natural brevenal. The key features of Sasaki's synthesis included a convergent assembly of the pentacyclic polyether skeleton by using a Suzuki-Miyaura cross coupling reaction. Also, the use of a CuTC promoted Stille reaction enabled Sasaki to stereoselectivity construct the left-hand (*E*,*E*)-diene system. Perhaps most importantly, Sasaki's total synthesis proved the correct stereochemistry of the C26 tertiary alcohol.

Kadota's synthesis

Kadota's total synthesis of brevenal is unique to the three syntheses of brevenal that are to be discussed, in that, Kadota used an intramolecular allylation followed by subsequent ring-closing metathesis to form the pentacyclic core of brevenal.[53] While certainly less convergent than Sasaki's synthesis, having a longest linear sequence of 57 steps, Kadota's introduction of the side chains was comparatively concise. Figure 1.14 illustrates Kadota's retrosynthetic analysis of brevenal. The side chains would be introduced by Wittig and Horner-Wadsworth-Emmons olefinations. The pentacyclic ether core would be synthesized from **1.49** via intramolecular allylation followed

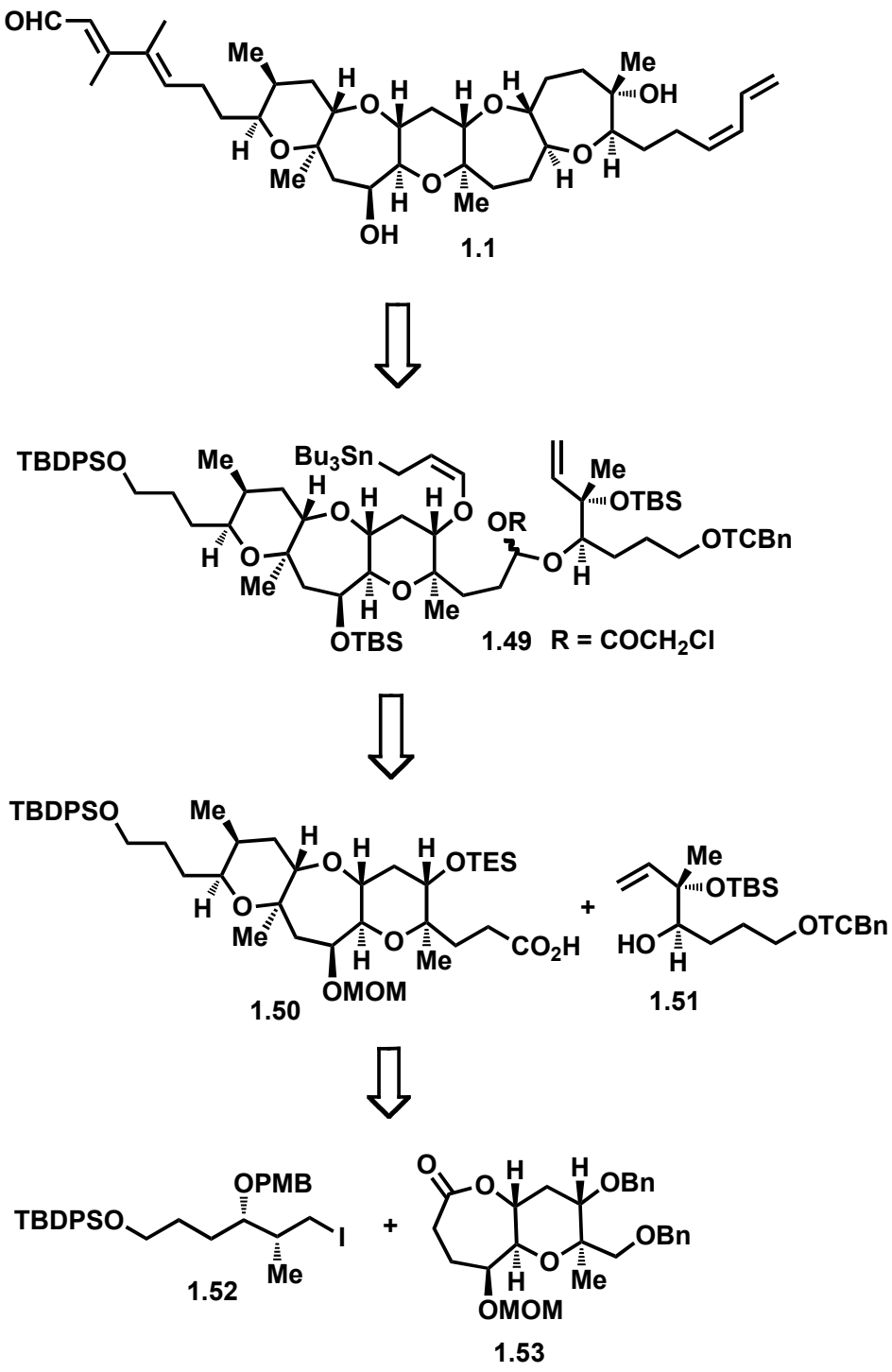


Figure 1.14. Kadota's retrosynthetic analysis.

by ring-closing metathesis. The cyclization precursor **1.49** was retrosynthetically divided into the ABC ring subunit **1.51** and the E ring subunit **1.51**. The tricycle **1.50** would be prepared from **1.52** and **1.53**.

Kadota's synthesis of the ABC subunit commenced with known compound **1.54**, which was prepared in four steps from 2-deoxy-*D*-ribose using Nicolau's procedure (Figure 1.15).[54] **1.54** was subjected to multiple protecting group manipulations to give **1.55**. Ozonolysis of the terminal olefin present in **1.55** provided the requisite aldehyde for the Brown asymmetric allylation, which gave **1.56** as a single stereoisomer in high yield. The resultant alcohol was protected as a MOM ether and several oxidation state manipulations provided the carboxylic acid **1.57**. Yamaguchi lactonization provided the B ring lactone, which was transformed to enol phosphate **1.58** in two additional steps.[38,55,56]

The enol phosphate **1.58** underwent a Suzuki-Miyaura coupling with the alkyl borate **1.59** to give **1.60** (Figure 1.16).[56] Hydroboration of **1.60** with BH_3 followed by oxidative workup gave the undesired stereoisomer **1.61** as the sole product. Kadota set out to invert the C11 stereochemistry. This was carried out by oxidation of **1.61** to the ketone followed by epimerization with DBU to provide the correct C11 stereoisomer. Deprotection of the PMB ether using DDQ furnished alcohol **1.62** in 89% yield over 4 steps. Next, the A ring was generated through a hydroxy-ketone cyclization to provide the corresponding mixed thioketal. The C12 angular methyl was installed analogously to Sasaki's synthesis: namely, through the oxidation of the thioacetal with *m*CPBA followed by treatment with $AlMe_3$ to give **1.63** as a single stereoisomer in good yield. [28,29,56] Seven additional steps were performed to give the ABC ring subunit **1.64**.

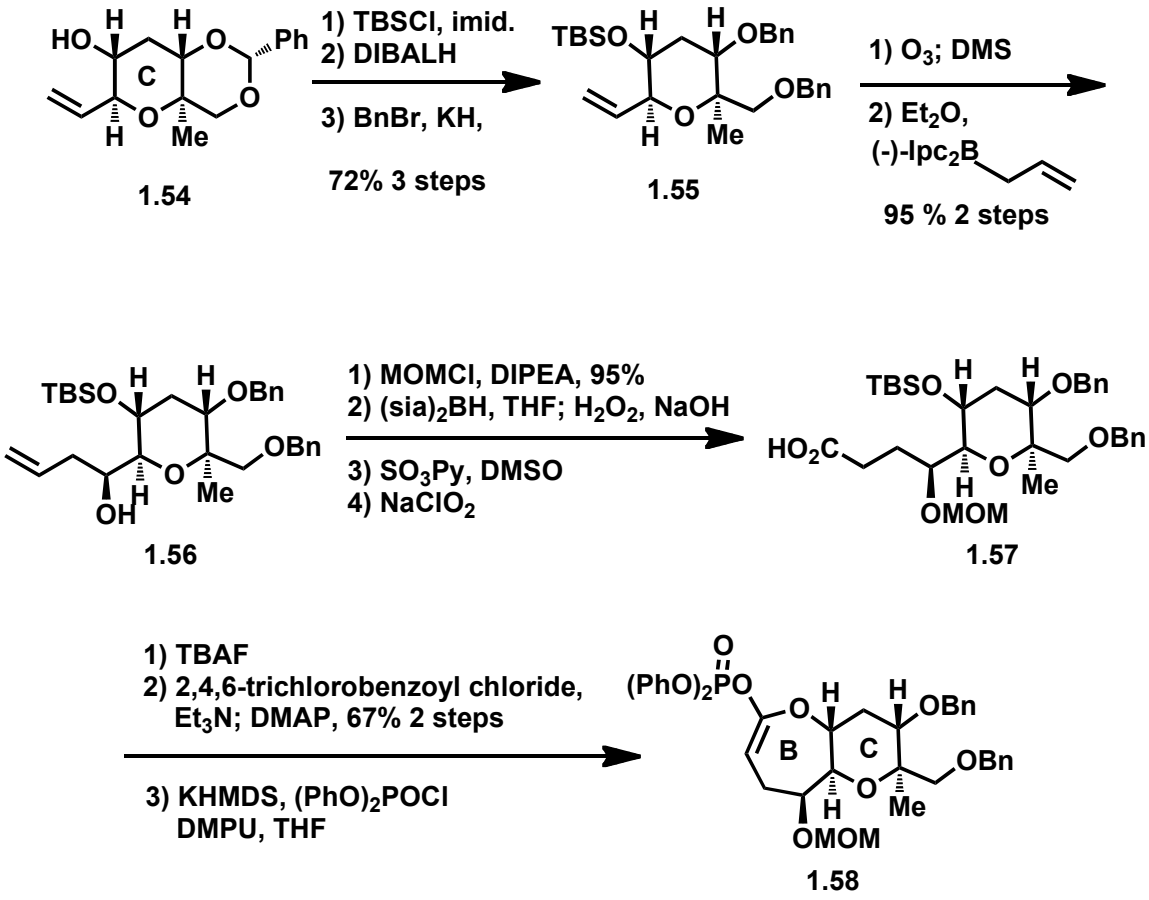


Figure 1.15. Synthesis of the BC-ring enol phosphonate.

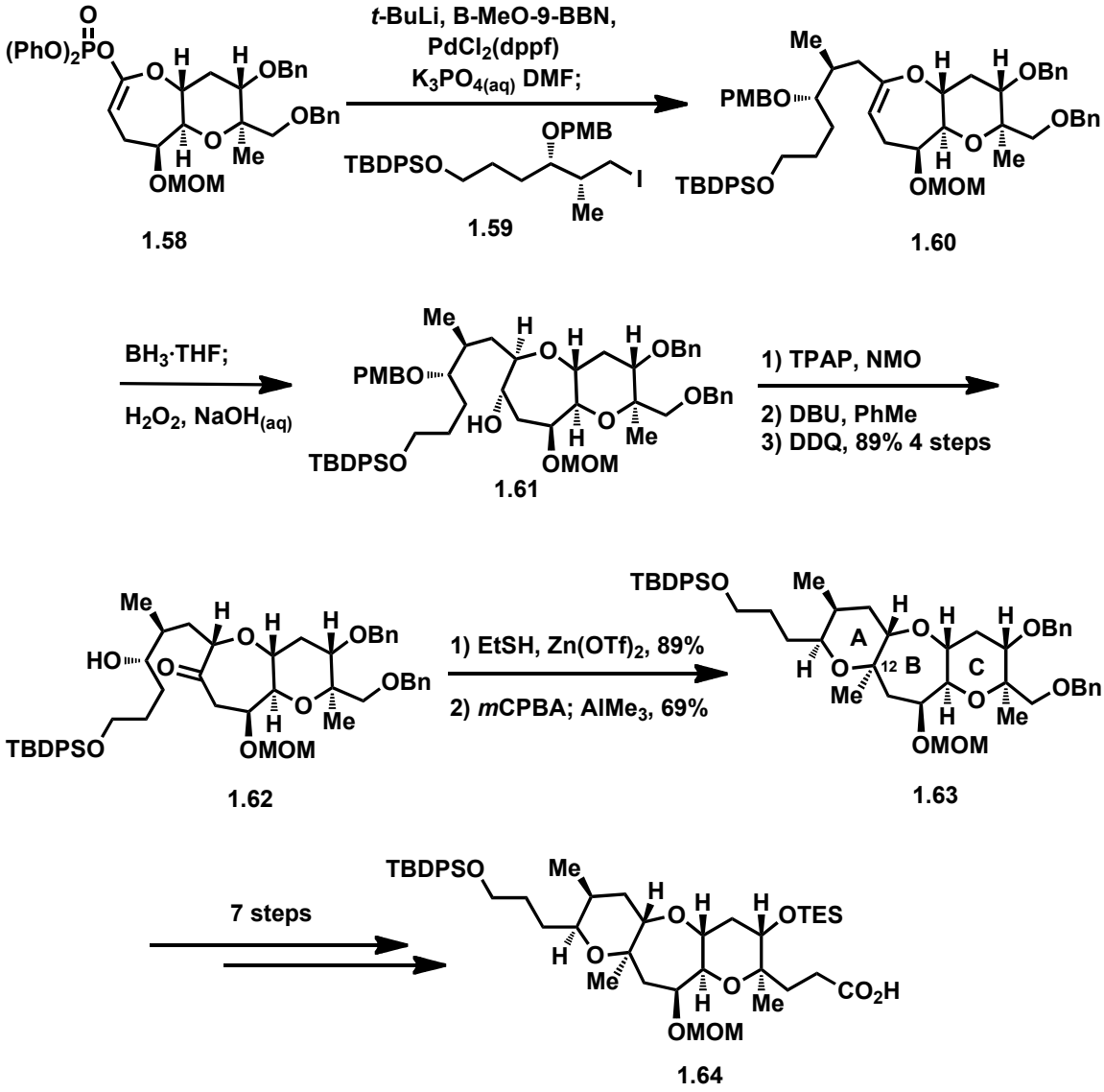


Figure 1.16 Construction of the ABC-ring system

The subunit coupling between the known carboxylic acid **1.64** and alcohol **1.51** was performed using Yamaguchi conditions to provide the ester **1.65**.[57,38] (Figure 1.17) The intramolecular allylation precursor **1.67** was obtained in four additional steps. The allyl tin compound underwent intramolecular allylation upon treatment with $MgBr_2 \cdot OEt_2$ to give **1.68** as a single stereoisomer. The pentacyclic core **1.69** was obtained through ring-closing metathesis of the diene **1.68** using Grubbs' second-generation catalyst. Kadota next examined the construction of the right-hand (*Z*)-diene side chain. To do this, the TCBn moiety needed to be deprotected. This proved troublesome under standard hydrogenolysis conditions (H_2/Pd-C). Kadota eventually found that the TcBn could be removed using Sajiki's dechlorination procedure (H_2/Pd-C, Et_3N) to give the benzyl ether.[58] Reduction of the E ring alkene with diimide followed by debenzylation and oxidation of the primary alcohol afforded **1.70**, which is an intermediate in Sasaki's synthesis.[28,29] The spectral data of **1.70** matched Sasaki's and prompted the group to append the side chains and complete the synthesis.

To append the right hand side chain, the primary alcohol in **1.70** was oxidized and the resulting aldehyde underwent reaction with the ylide **1.47**.[51,52] An oxidative work up provided the diene **1.71** as a single stereoisomer in good yield. (Figure 1.18). Next, the installation of the A-ring side chain was attempted. Kadota's method involved using a Horner-Wadsworth-Emmons reagent generated from **1.72** to stereoselectivity install the highly substituted (*E,E*)-diene moiety. Ester **1.73** was then reduced and the remaining silyl groups were removed. The allylic alcohol was then chemoselectivity oxidized using MnO_2 to complete the synthesis of brevenal. Kadota makes note that the synthetic brevenal matched the spectral data of natural brevenal.

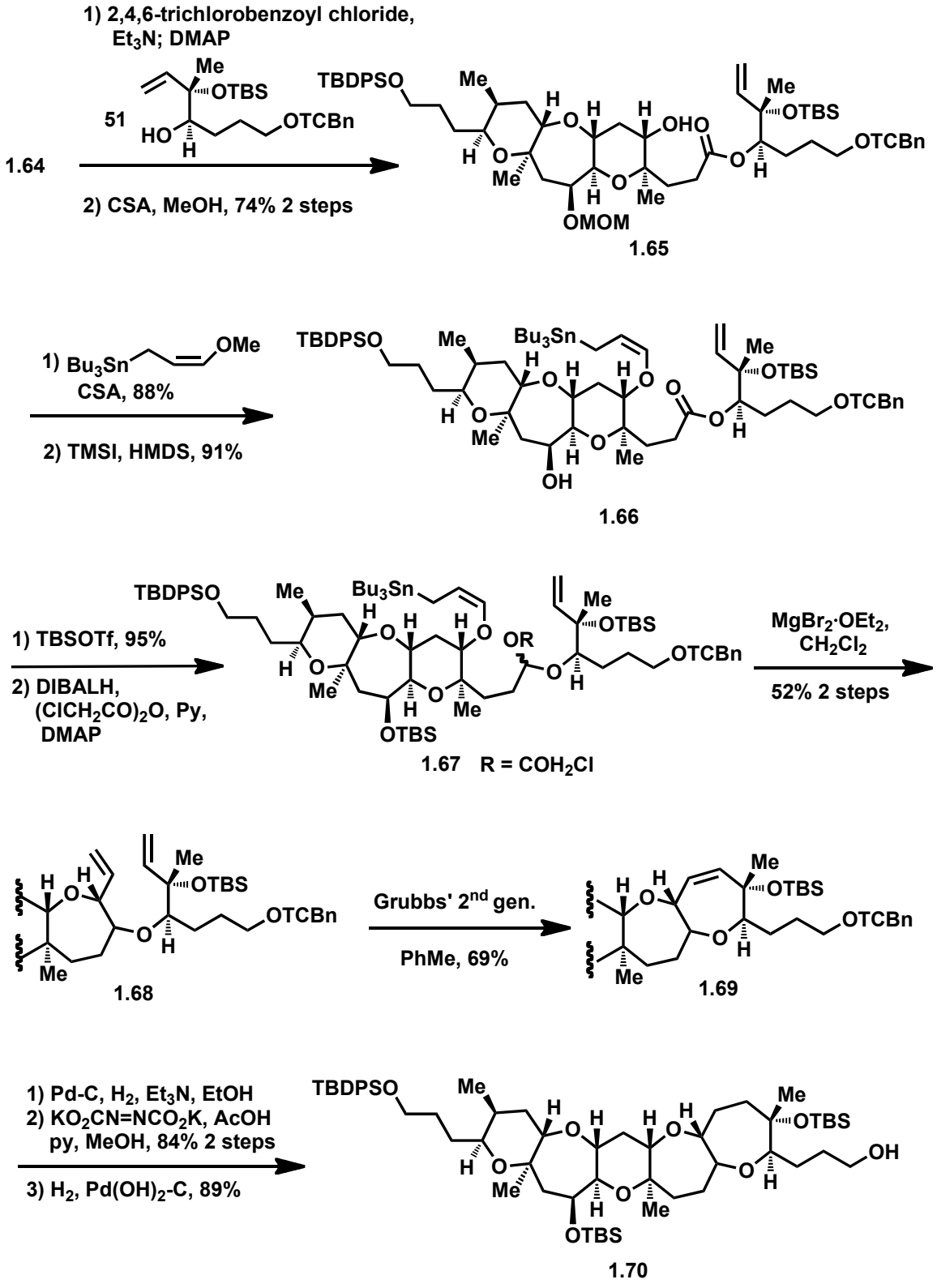


Figure 1.17. Completion of brevenal's pentacyclic core.

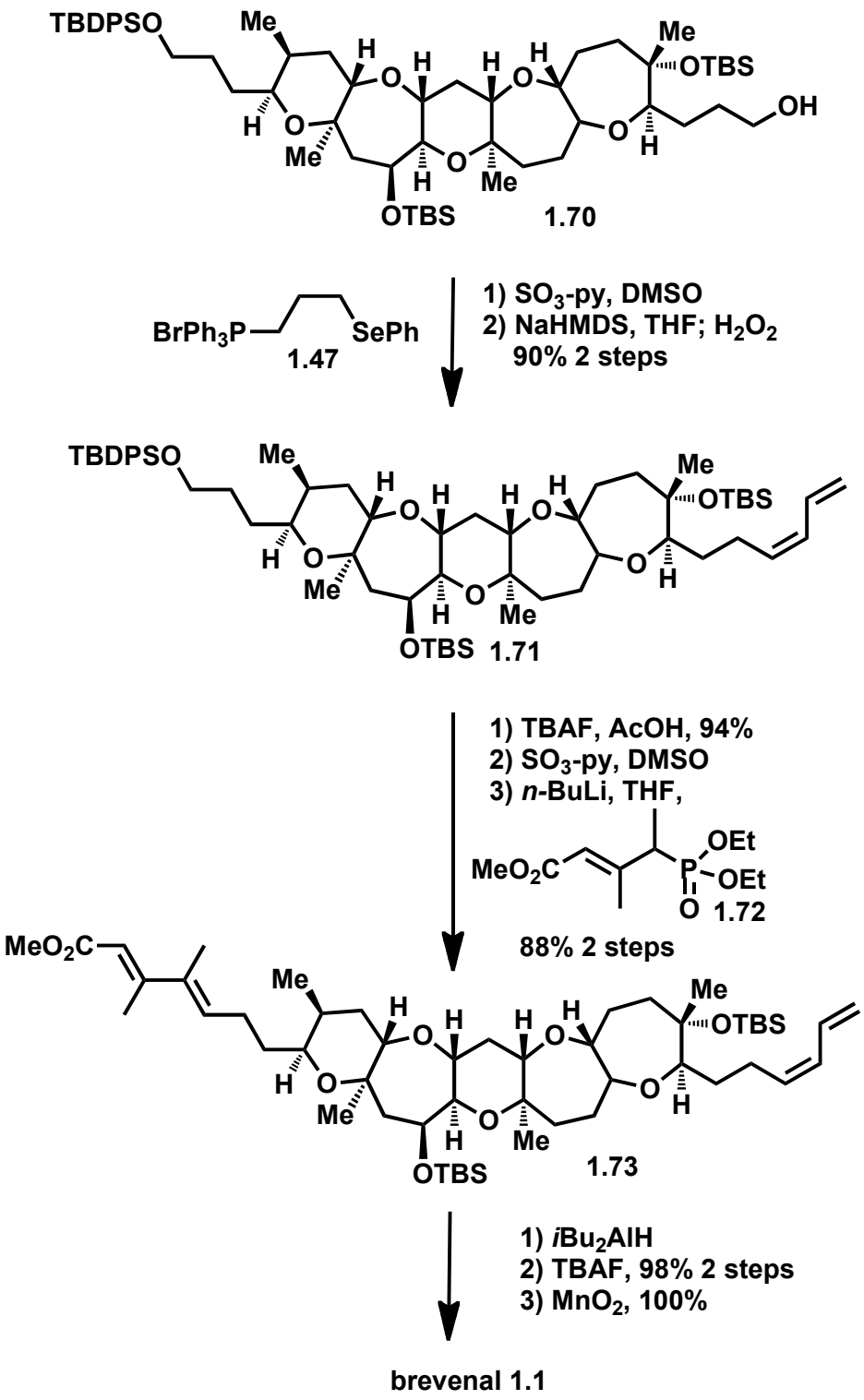


Figure 1.18. Installation of the side chains and completion of the synthesis.

The key features of Kadota's synthesis include an intramolecular allylation to form the pentacyclic polyether skeleton of brevenal and the stereoselective construction of the left-hand multi-substituted (*E*,*E*)-diene system through an Horner-Wadsworth-Emmons reaction. Overall, the synthesis contained a longest linear sequence of 57 steps with an overall yield of 0.84%. Although Kadatoa's synthesis is lengthier, his side chain installation is comparatively concise compared to Sasaki's methods.

Crimmins' partial synthesis

The most recent synthetic work that has been reported towards brevenal was Crimmins' partial synthesis published in 2010. In brief, his work described the synthesis of an advanced intermediate using a convergent strategy. Although he has not completed the synthesis to date, his group has taken an interesting approach toward the molecule that warrants discussion.

Crimmins' retrosynthetic analysis follows the usual protocol of installing the sensitive side chains late in the synthesis (Figure 1.19). He does not, however, go into the intricate details of their installation since his group has not reached that point in the synthesis. An acid catalyzed cyclization followed by dehydration of the enone-alchol system in **1.75** was proposed to form the D ring **1.74**. The Horner-Wadsworth-Emmons union of the AB ketophosphonate **1.76** and the E ring containing aldehyde **1.77** was to give **1.75**. Crimmins' construction of AB ketophosphonate **1.76** and E ring aldehyde **1.77** is centered on the ring-closing metathesis approach to medium sized rings.[60,61]

The synthesis commenced with a diastereoselective Evans' aldol addition between phenylalanine derivative **1.78** and aldehyde **1.79** to give the

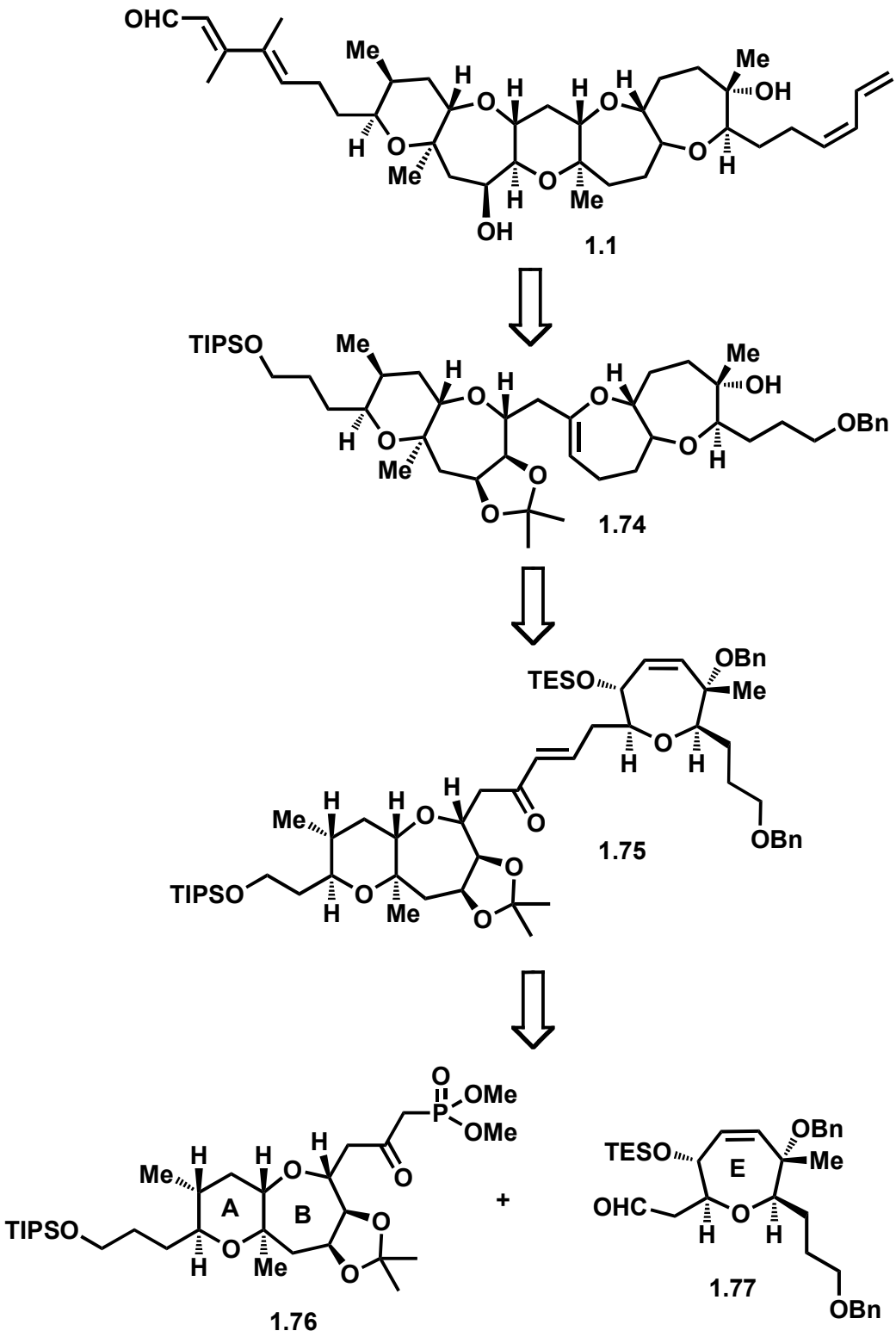


Figure 1.19. Crimmins' retrosynthetic analysis

1,2-*syn* product **1.80** (Figure 1.20).[62] The secondary alcohol of **1.80** was TMS protected and the auxiliary was cleaved under reductive conditions to give aldehyde **1.81**. A Horner-Wadsworth-Emmons coupling of β-ketophosphonate **1.82** with aldehyde **1.81** provided the enone **1.83** in 90% yield as a single isomer.[63] The α,β–unsaturation present in **1.83** was reduced using *i*BuAlH and MeCu and the TMS ether was removed to generate the A ring precursor **1.84**.[64] Subjection of **1.84** to cyclodehydration conditions provided enol ether **1.85** in excellent yield. Using Sasaki's procedure, the angular methyl was installed through an epoxidation/thioketal formation and its oxidation to the corresponding sulfone.[28] The sulfone was then displaced with retention of stereochemistry using $AlMe_3$ to give **1.87**. Reductive removal of the benzyl group and oxidation gave the corresponding aldehyde.[65] Olefination of the aldehyde followed by TES deprotection gave **1.88**.

With the requisite stereochemistry of the A-ring installed, the construction of the B ring was pursued (Figure 1.21). To do this, Crimmins used his glycolate alkylation/ring-closing metathesis strategy.[60,61] This strategy nicely sets the B-ring stereochemistry and provides a handle for the introduction of the C13/C14 hydroxyl groups. To access glycolate alkylation precursor **1.91** the secondary alcohol **1.89** was alkylated with bromoacetic acid in the presence of sodium hydride. The glycolic acid was converted to the mixed pivalic anhydride and treated with the lithiate of the valine derived auxiliary **1.90** to give oxazolidinone **1.91**. Diastereoselective alkylation of the sodium enolate of **1.91** with bromoacetonitrile provided the nitrile in 58% yield. The chiral auxiliary was removed under reductive conditions to provide primary alcohol **1.92** which was oxidized to provide diene after Wittig olefination. Treatment of diene **1.93** with Grubbs' second

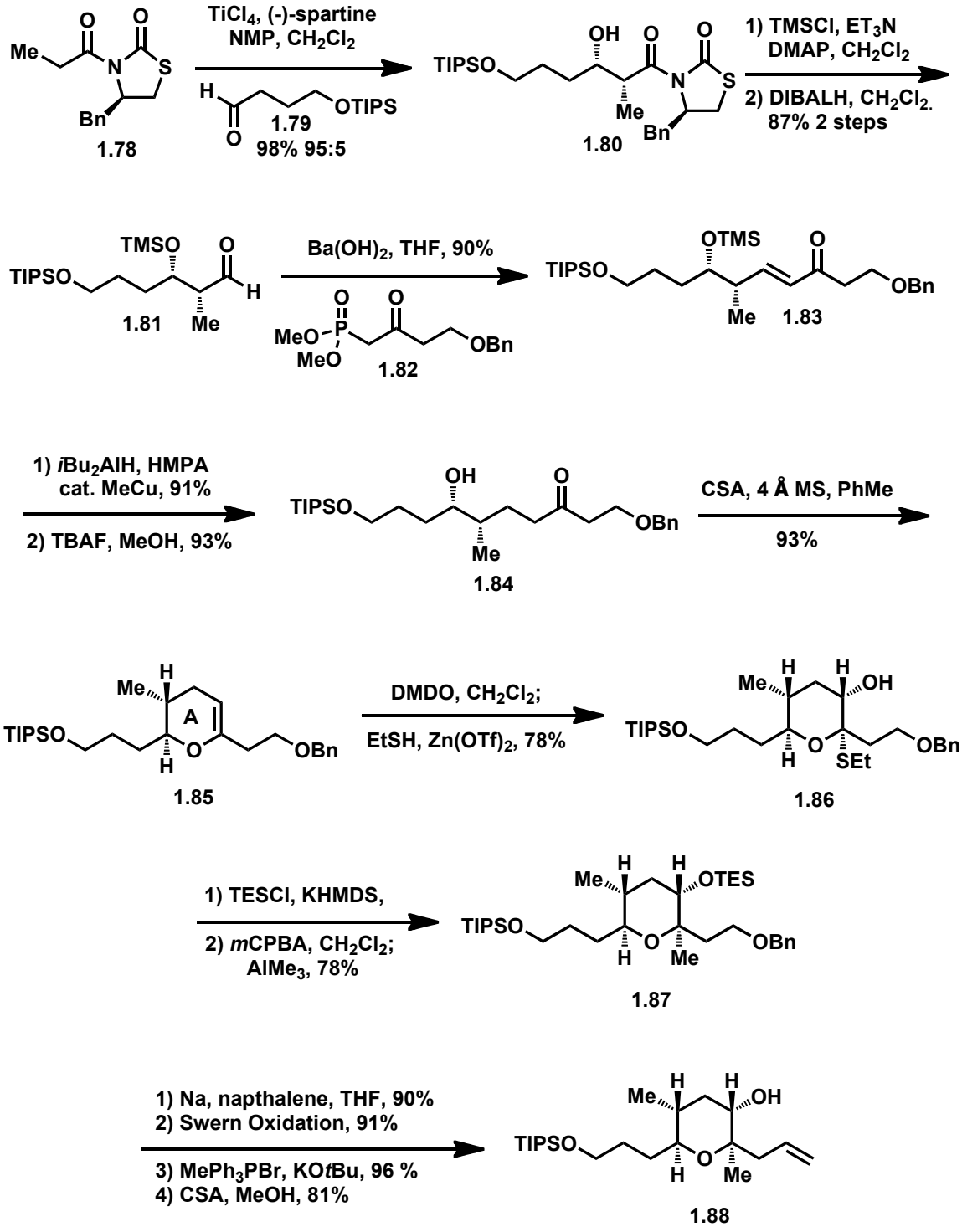


Figure 1.20. Synthesis of the A-ring.

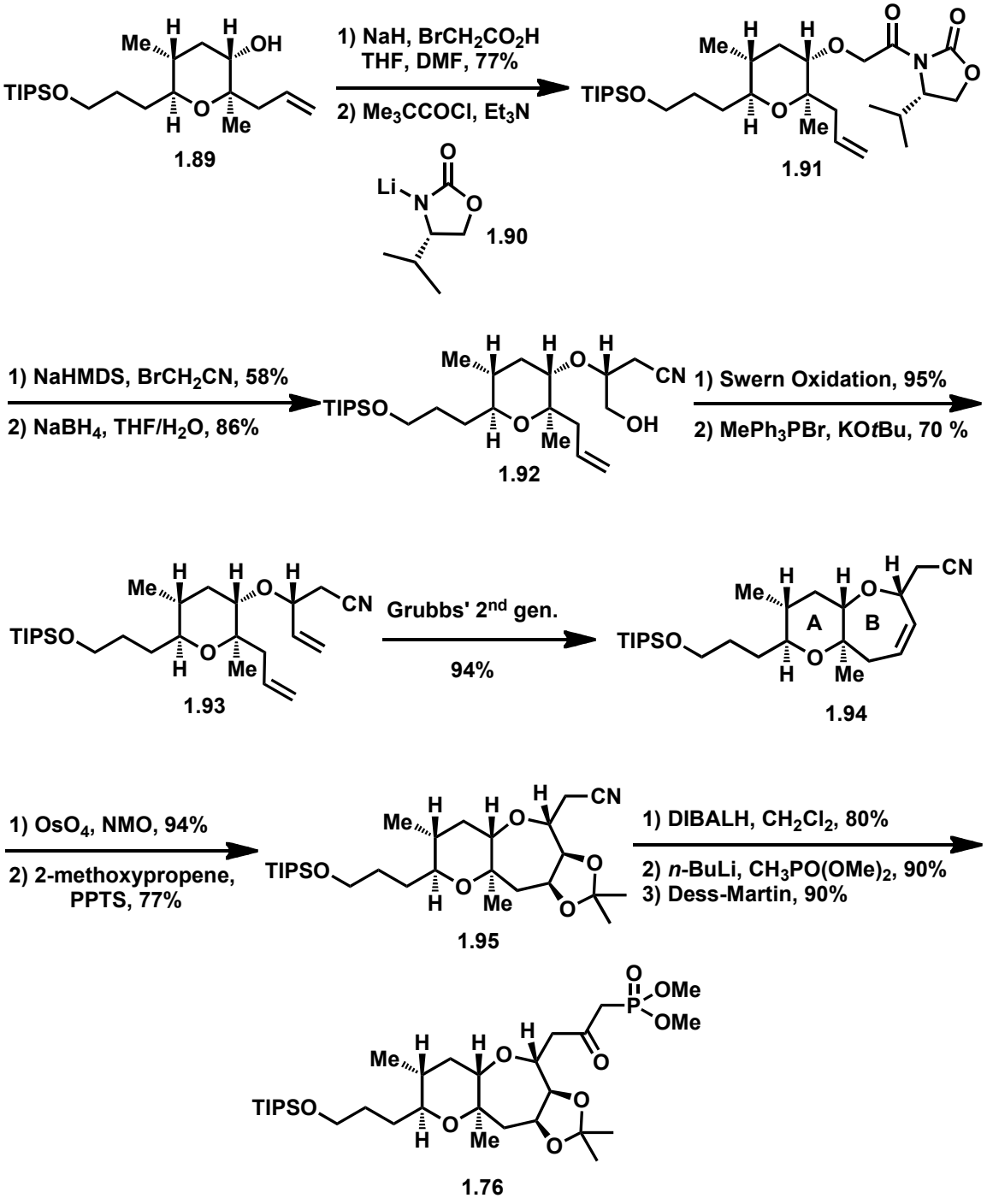


Figure 1.21. Formation of the AB ring system coupling precursor.

generation catalyst provided the AB bicycle **1.94** in excellent yield. By taking advantage of the olefin generated from the metathesis reaction, the C13/C14 diol was able to be installed through a highly diasteroselective dihydroxylation reaction. The diol was protected as the dimethyl acetonide **1.95** and its relative stereochemistry was confirmed by NOESY analysis. Next, the nitrile was reduced using *i*BuAlH to give the corresponding aldehyde, which was converted to the coupling precursor **1.76** in two additional steps. The AB-ring fragment was completed in 27 steps (longest linear sequence).

Efforts then focused on the synthesis of the E ring aldehyde **1.77** (Figure 1.22). An asymmetric aldol addition between oxazolidinone **1.96** and aldehyde **1.97** was used to set the C26 tertiary alcohol stereocenter providing **1.98** with superb diastereoselectivity (95:5 dr).[66] The auxiliary was converted to the methyl ester, and the free hydroxyl group was protected as a TES ether. The conversion of the methyl ester to aldehyde **1.99** was completed using a two-step reduction/oxidation sequence. After generation of the terminal olefin from the aldehyde functionality through a Wittig reaction, the TES group was removed to furnish alcohol **1.100**. Crimmins used the analogous strategy that served to establish the B ring stereochemistry to create sterogenic centers in the E ring.[60,61] Alkylation of **1.100** with bromoacetic acid followed by coupling with oxazolidinone lithiate **1.90** provided glycoyl oxazolidinone **1.101** in 88% yield. Generation of the sodium enolate of **1.101** followed by alkylation with bromoacetonitrile produced the nitrile with excellent diastereoselectivity (95:5 dr). Reductive removal of the auxiliary then furnished the primary alcohol **1.102**. The resultant hydroxyl group was oxidized to the aldehyde under Swern conditions and was then treated with divinyl zinc to give

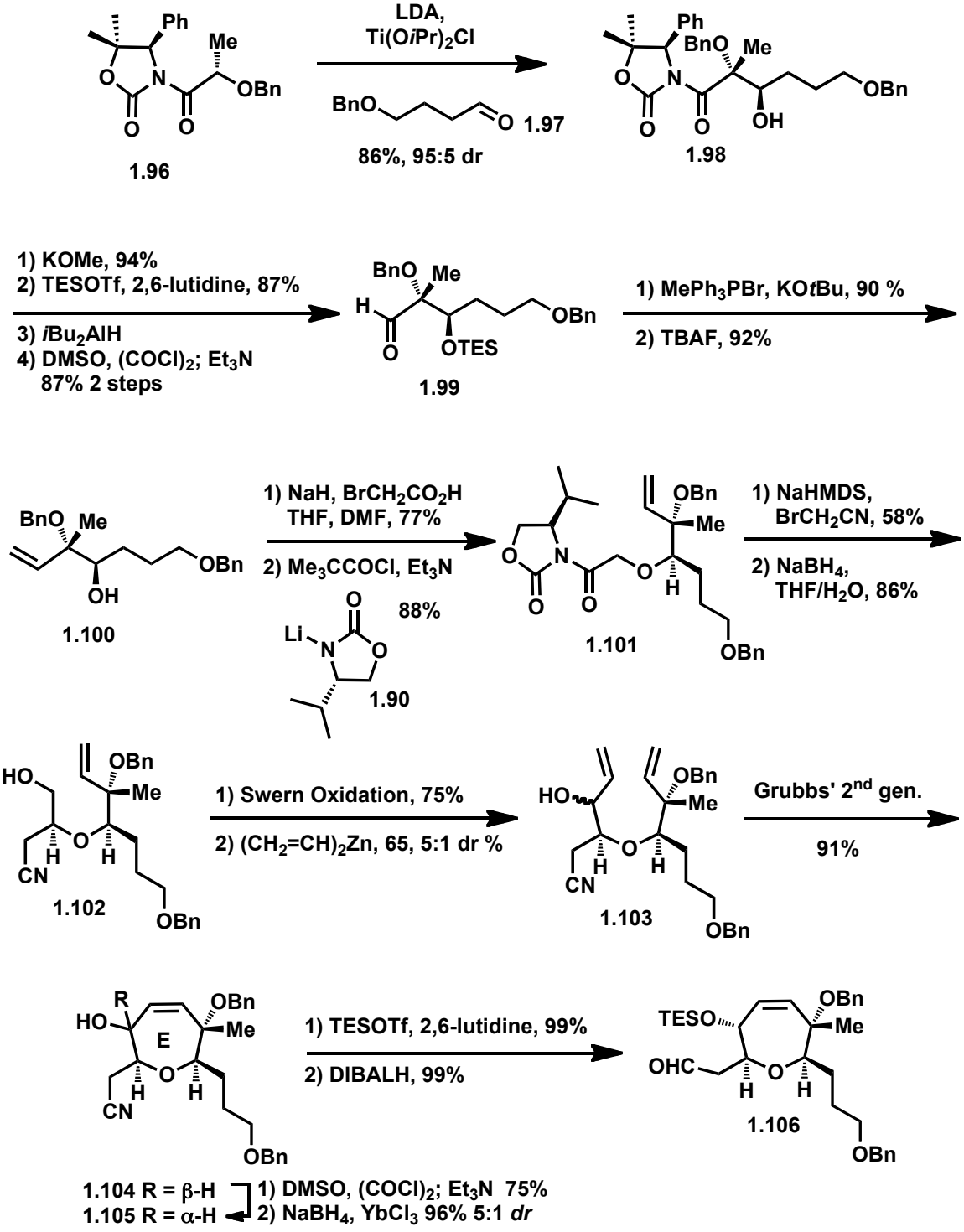


Figure 1.22. Synthesis of the E-ring system.

a mixture of diastereomers **1.103**.[65] Exposure of this diastereomeric mixture to Grubbs' second generation catalyst gave the epimeric cyclic ethers **1.104** and **1.105**. The undesired diastereomer **1.104** could be converted to **1.105** via an oxidation/reduction sequence. Protection of **1.105** as a TES ether and reduction of the nitrile generated E-ring aldehyde **1.77**.

With both the AB ring β-ketophosphonate and E ring aldehyde prepared, attention was directed toward coupling of the fragments and completing brevenal. β-ketophosphonate **1.76** and aldehyde **1.77** were coupled using a Horner-Wadsworth-Emmons reaction to provide the enone **1.75** in excellent yield (Figure 1.23)

As this point in the synthesis, Crimmins' envisioned that the formation of the D ring could be achieved through an acid-catalyzed cyclodehydration. Manipulation of the resulting enol ether **1.74** and formation of the C-ring could give the pentacyclic polyether core. Installation of the left- and right-hand side chains will then furnish brevenal **1.1**.

In summary, Crimmins' reported a convergent and unique approach toward the total synthesis of brevenal. Utilizing the asymmetric glycolate alkylation/ring-closing metathesis method, both coupling fragments were synthesized. Crimmon's efforts to complete the carbon framework and elaborate the side chains are ongoing in his laboratory.

Results and Discussion

The structural complexity and intriguing biological activities of marine polycyclic ether natural products prompted our group to initiate a program directed towards their synthesis. Through the development of an iterative synthetic strategy our research group

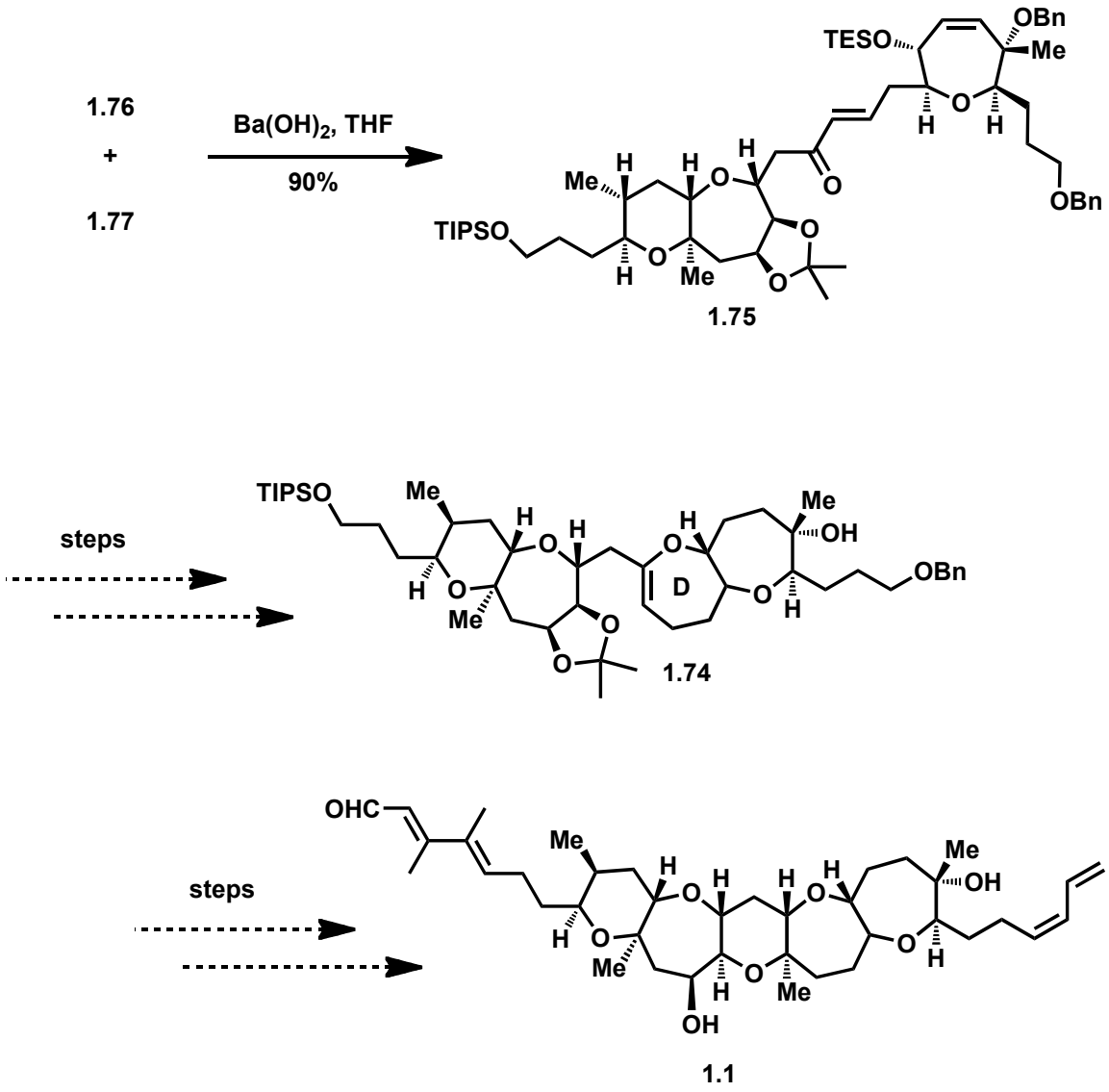


Figure 1.23. Horner-Wadsworth-Emmons reaction of **1.76** and **1.77**.

has synthesized a number of polycyclic ether natural products and analogues. Representative examples include the total synthesis of gambeierol,[67] the formal synthesis of hemibrevetoxin B and its analogues,[68,69] the A-E ring system of gambieric acid A, [70] the partial synthesis of adriatoxin,[71] and the total synthesis of brevenal.[72]

The basis of our strategy for the assembly of these molecules relies on three synthetic transformations as depicted in Figure 1.24: 1) the generation of a *C*-glycoside and/or *C*-ketoside **1.106**, **1.107** through an oxidation/nucleophillic addition of an enol ether **1.108**; 2) the synthesis of cyclic enol ethers **1.109** through olefinic-ester ring-closing metathesis from the appropriate cyclization precursor **1.107**, and; 3) the synthesis of cyclic enol ethers **1.110** using an acid catalyzed cyclization/elimination from substrates similar to **1.106**.[27] In the context of these reactions, the development of a synthesis that allows rapid access to the pentacyclic core structure of brevenal was proposed and the details of the approach are presented herein.

Our synthetic strategy chosen for brevenal is depicted in Figure 1.25. As with all of previously published syntheses, we planned a late stage introduction of the sensitive diene and dienal side chains after the pentacyclic core of brevenal had been constructed.[28,29,53] The generation of the D ring and completion of the core was envisioned to be possible through a reductive cyclization from the corresponding hydroxy ketone. The C ring was to be formed using our reduced titanium ethylidene reagent to effect the olefinic-ester cyclization of **1.113**.[73] At this point, we have chosen to retrosynthetically bifurcate **1.113** into the AB subunit **1.114** and the E ring subunit **1.115** thereby making the synthesis highly convergent. Their coupling was planned through an esterification reaction. The AB ring **1.114** was thought to be available through an acid mediated

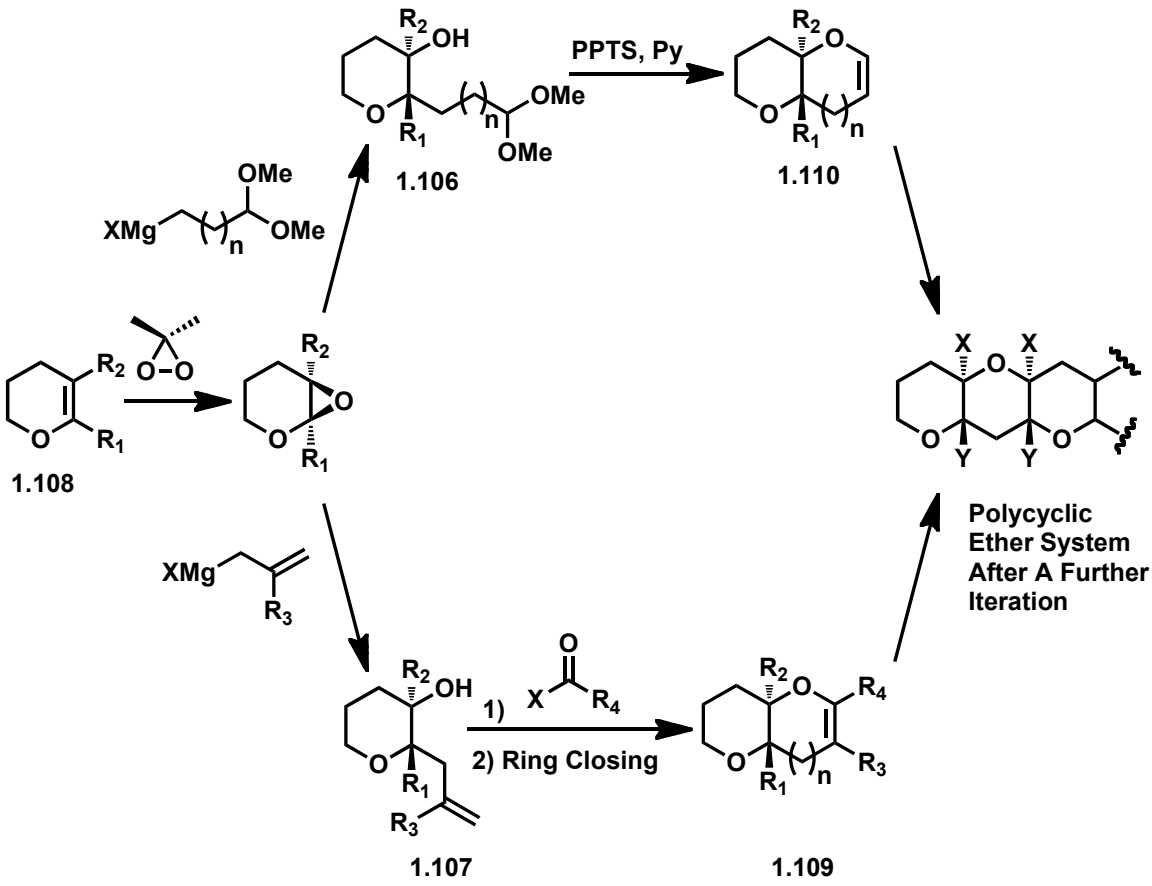


Figure 1.24. Our current strategy for the construction of polycyclic ether natural products.

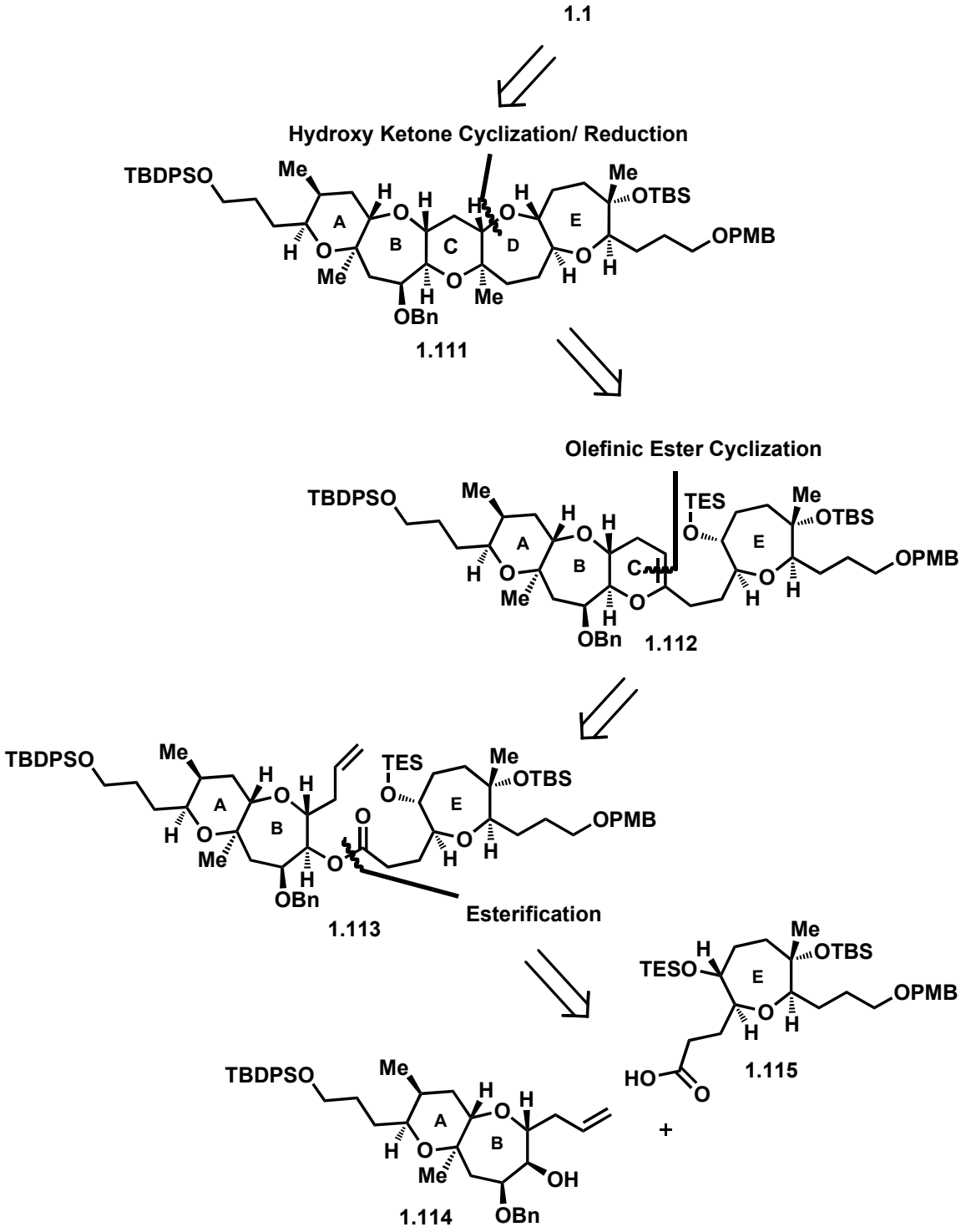


Figure 1.25. Retrosynthesis of brevenal

cyclization/elimination sequence of **1.115** (Figure 1.26). The A ring enol ether would be generated from olefinic-ester substrate **1.116**. The 1,2-*syn* stereochemistry present in **1.116** would be established through a Brown crotylation reaction of aldehyde **1.117**.[74] As for the E ring, the olefinic-ester substrate **1.120** would provide the requisite oxepene ring that would then be oxidized and reduced to provide a handle for setting the C26 tertiary alcohol. The 1,2-*trans*-stereochemistry in **1.120** was to come from glyceraldeyhyde derivative **1.121**.

In this chapter, the stereoselective syntheses of the AB ring and the E ring fragments will first be presented. A discussion of the union of the two fragments, synthesis of the pentacyclic core and completion of the molecule will then follow.

Synthesis of the AB ring Fragment

At the outset of this project, Dr. Henry Johnson established a synthetic route to the A ring through model studies.[75] Although our strategy for the synthesis of the A ring was later modified for material throughput purposes, the model study was important for the completion of the molecule and warrants discussion. The synthesis of the A ring model system is shown in Figure 1.27. A Brown crotylation performed on aldehyde **1.122** delivered the requisite 1,2-*syn* alcohol **1.123** in 90% yield and 86% *ee*.[74] The absolute stereochemistry of **1.123** was established through Mosher ester analysis.[76] The alcohol **1.123** was subjected to esterification conditions using DCC/DMAP to obtain ester **1.124** in 85% yield. A three-step one-carbon homologation involving: 1) hydroboration and oxidative work-up followed by; 2) oxidation to the aldehyde, and; 3) Wittig reaction provided the cyclization precursor **1.125**. Subjection of the olefinic ester **1.125** to the

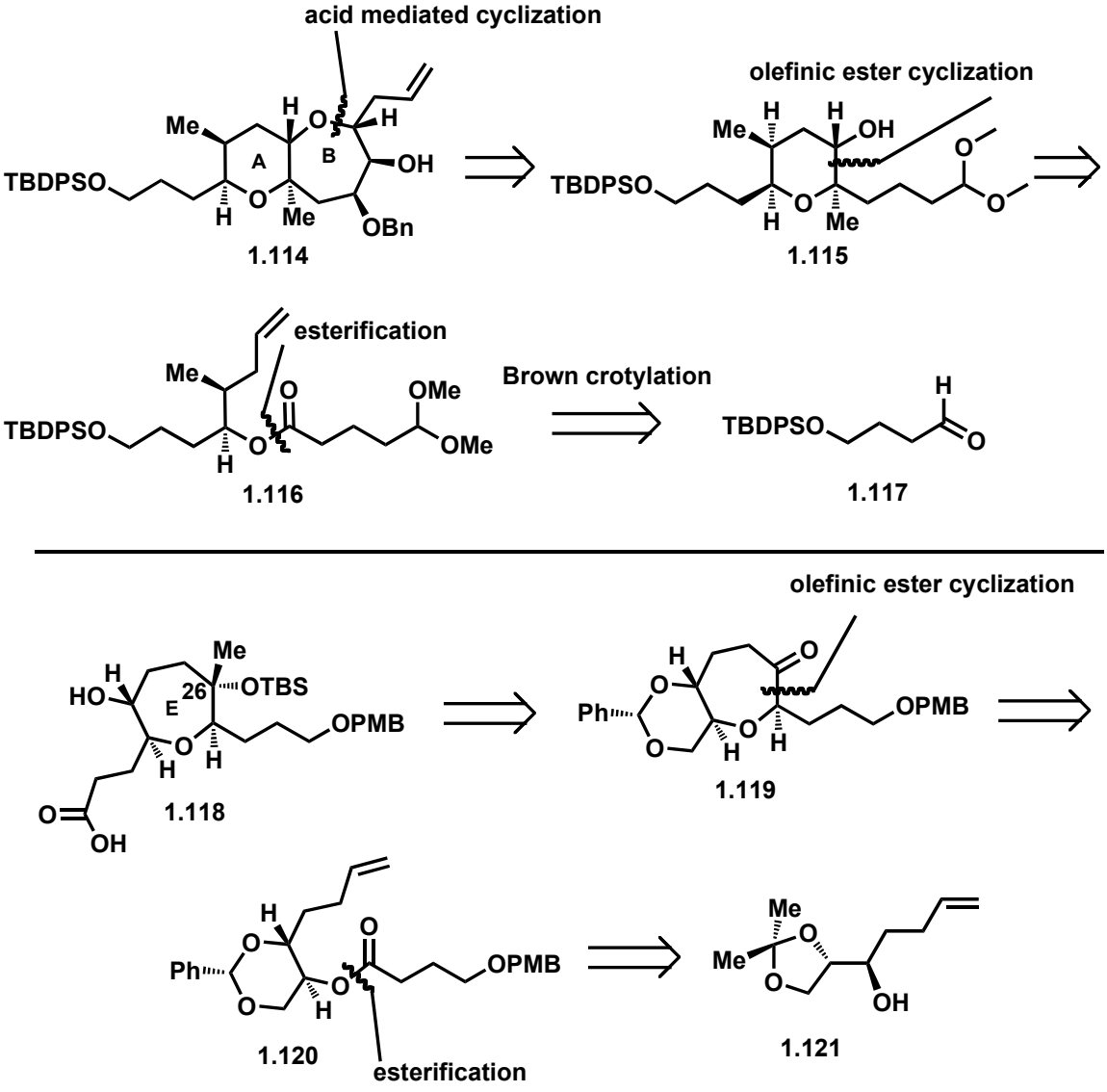


Figure 1.26. Olefinic-ester precursors to the AB and E ring fragments.

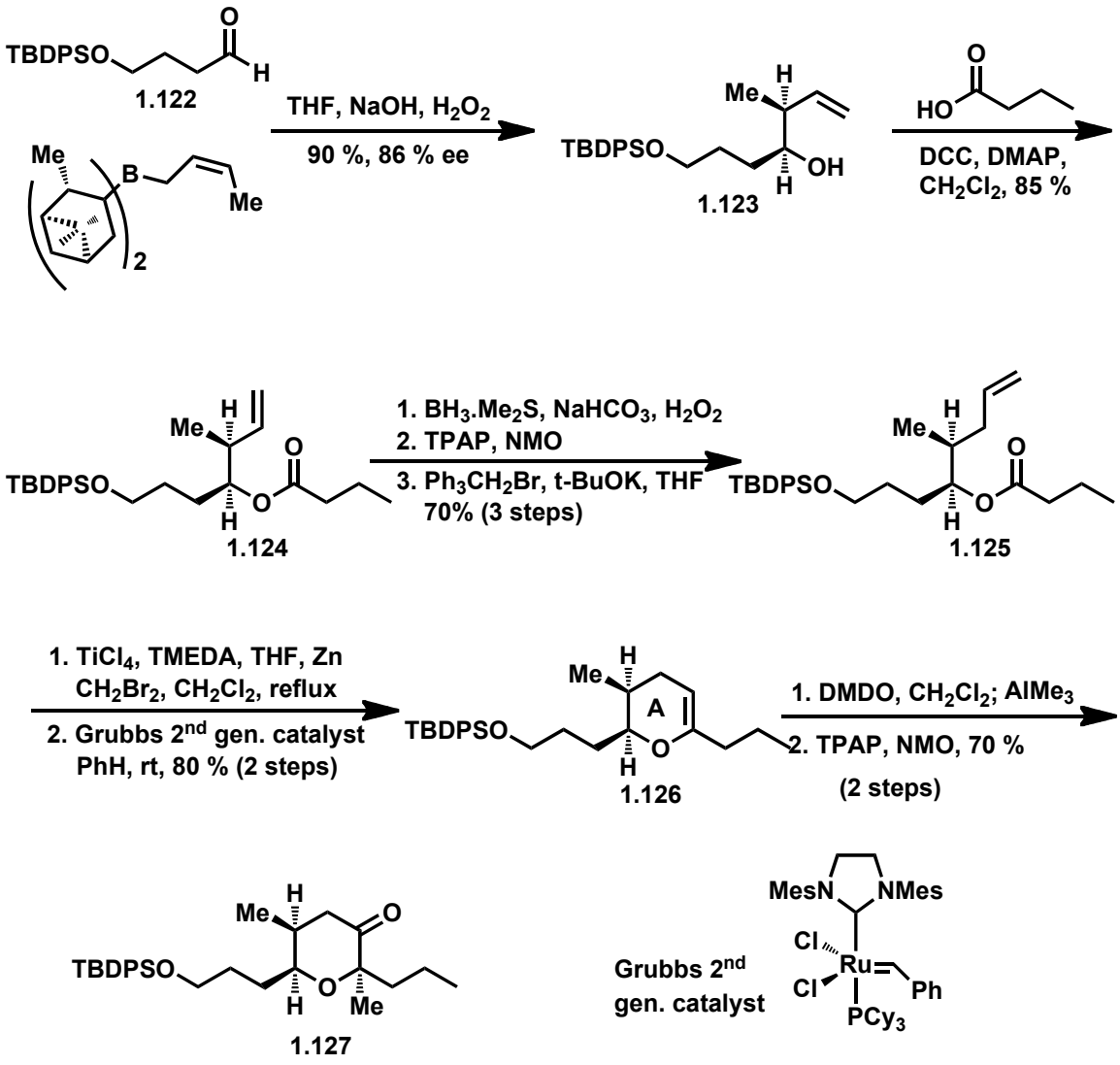


Figure 1.27. Model studies of the A ring.

Takai-Utimoto reaction led to the formation of the corresponding acyclic enol ether. This was then treated with Grubbs' second-generation catalyst to obtain cyclic enol ether **1.126** in 80% yield over two steps. Oxidation of the enol ether with dimethyl dioxirane (DMDO) followed by immediate addition of $AlMe_3$ led to the desired alcohol. Oxidation of the secondary alcohol to the ketone using TPAP and NMO occurred in 70% yield over two steps.[43] The relative stereochemistry of **1.127** was confirmed by nOe analysis.

The stereochemical outcome of the DMDO/$AlMe_3$ reaction is rationalized in Figure 1.28. The epoxide **1.132** generated from the reaction of DMDO with glycal **1.128** results from the epoxidation of the more abundant conformer **1.130**. Although **1.130** and **1.129** are in equilibrium, the bow-tie conformer **1.130** has the large -$(CH_2)_4$OTBDPS pseudoequatorial and will be present in greater concentration. The epoxidation of **1.128** is asynchronous and occurs from the α-face due to unfavorable steric interactions between the C12 pseudoaxial methyl with the approaching DMDO molecule. Next, *syn* addition of the methyl to the epoxide **1.132** occurs through complexation of $AlMe_3$ to provide **1.133**. Intramolecular methyl transfer to the oxonium ion then gives the product **1.134** after workup.[76]

These initial model studies validated our strategy and encouraged us to carry out the synthesis of the AB ring diol **1.114** as per our retrosynthetic analysis shown in Figure 1.26. Similar to our model studies, our synthesis of the AB diol **1.114** commenced with the crotyl adduct **1.123** (Figure 1.29). Esterification with the known carboxylic acid **1.135** bearing the dimethylacetal moiety gave **1.136**. The three-step one-carbon homologation sequence was employed to give olefinic ester **1.138**.

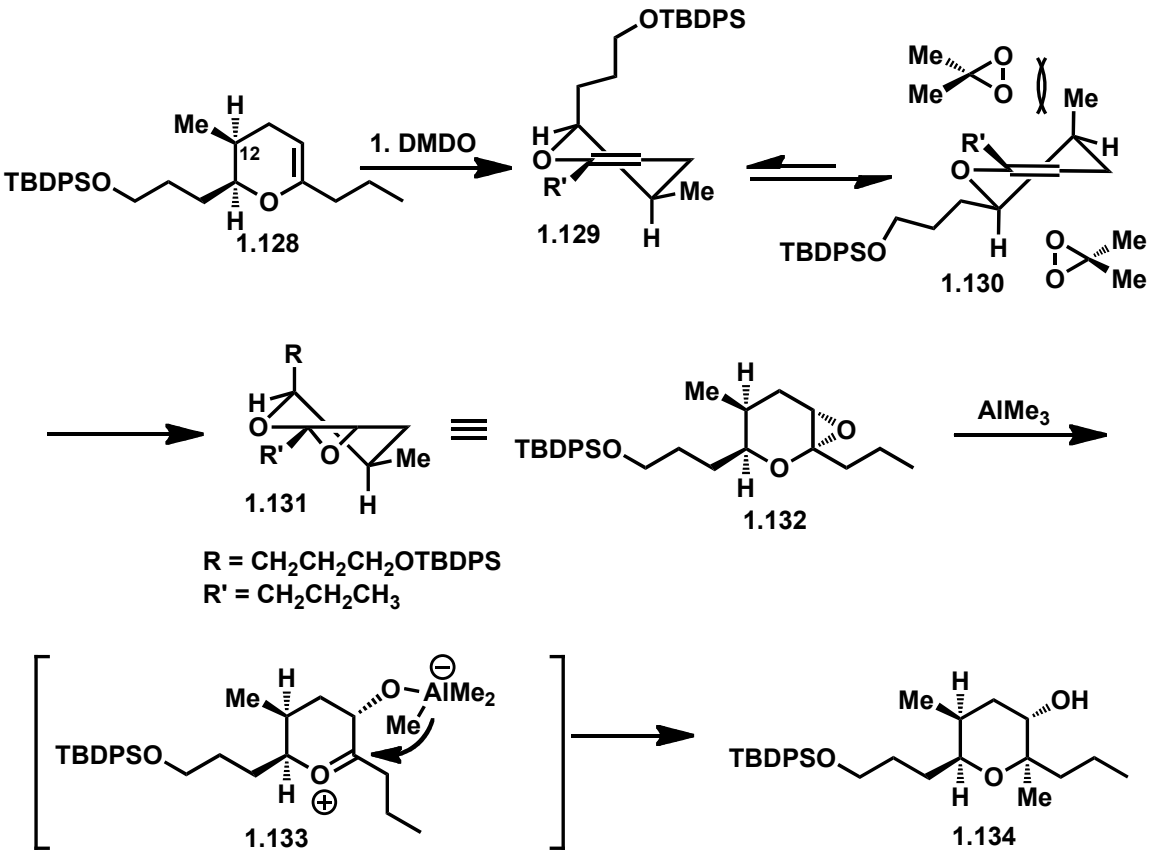


Figure 1.28. Proposed stereochemical rationale for epoxidation and $AlMe_3$ addition.

The modest yield over the three reactions is attributed to the hydrolysis of the ester during the alkaline oxidative workup that follows the hydroboration to give diol **1.137**. As demonstrated by Dr. Karthik Iyer, **1.137** could be recovered and transformed into the primary alcohol **1.138** in three steps that included: 1) chemoselective TES protection of the primary alcohol; 2) esterification of the secondary alcohol, and; 3) selective deprotection of the TES group (Figure 1.30).[77]

Keeping in mind the need for this process to be amenable to scale, a more direct and simple approach was investigated that would bypass the formation of the diol **1.137**. The obvious more efficient way to bypass the hydrolysis of the ester was to protect the secondary alcohol present in **1.123** with a group orthogonal to the TBDPS, such as a PMB group and delay the esterification until after the alkene has been homologated. Conditions to make the PMB ether were investigated and it was found that a concentrated reaction mixture and the use of KH as base gave the product **1.142** in excellent yield (Figure 1.31).

Next, the three-step one-carbon homologation sequence was employed to provide **1.143** in 73% yield over three steps; a significant improvement with respect to the process outlined in Figures 1.29 and 1.30. The success of these reactions allowed us to scale this sequence to a point where Brown crotylations were performed on a 90.0 gram scale allowing for significant quantities of **1.143** to be made. We next subjected the homologated product **1.143** to DDQ to oxidatively remove the PMB group to afford the secondary alcohol in 92% yield. Esterification of the secondary alcohol occurred quantitatively when an excess of the carboxylic acid **1.135** was used.

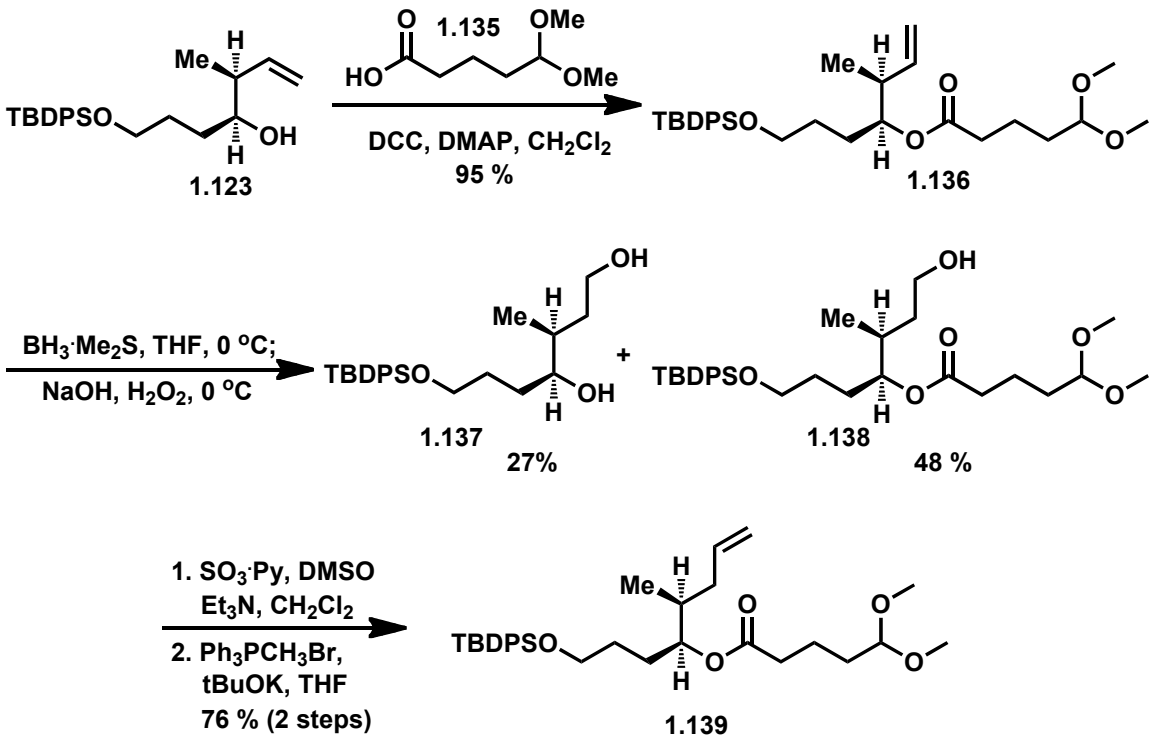


Figure 1.29. Generation of the cyclization precursor **1.139**.

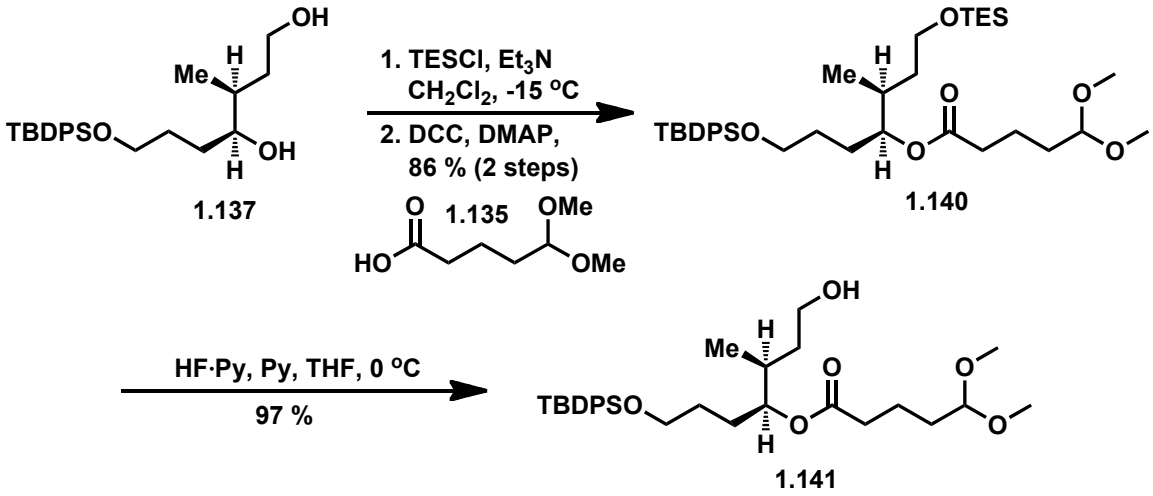


Figure 1.30. Recycling of byproduct **1.137** to generate **1.141**.

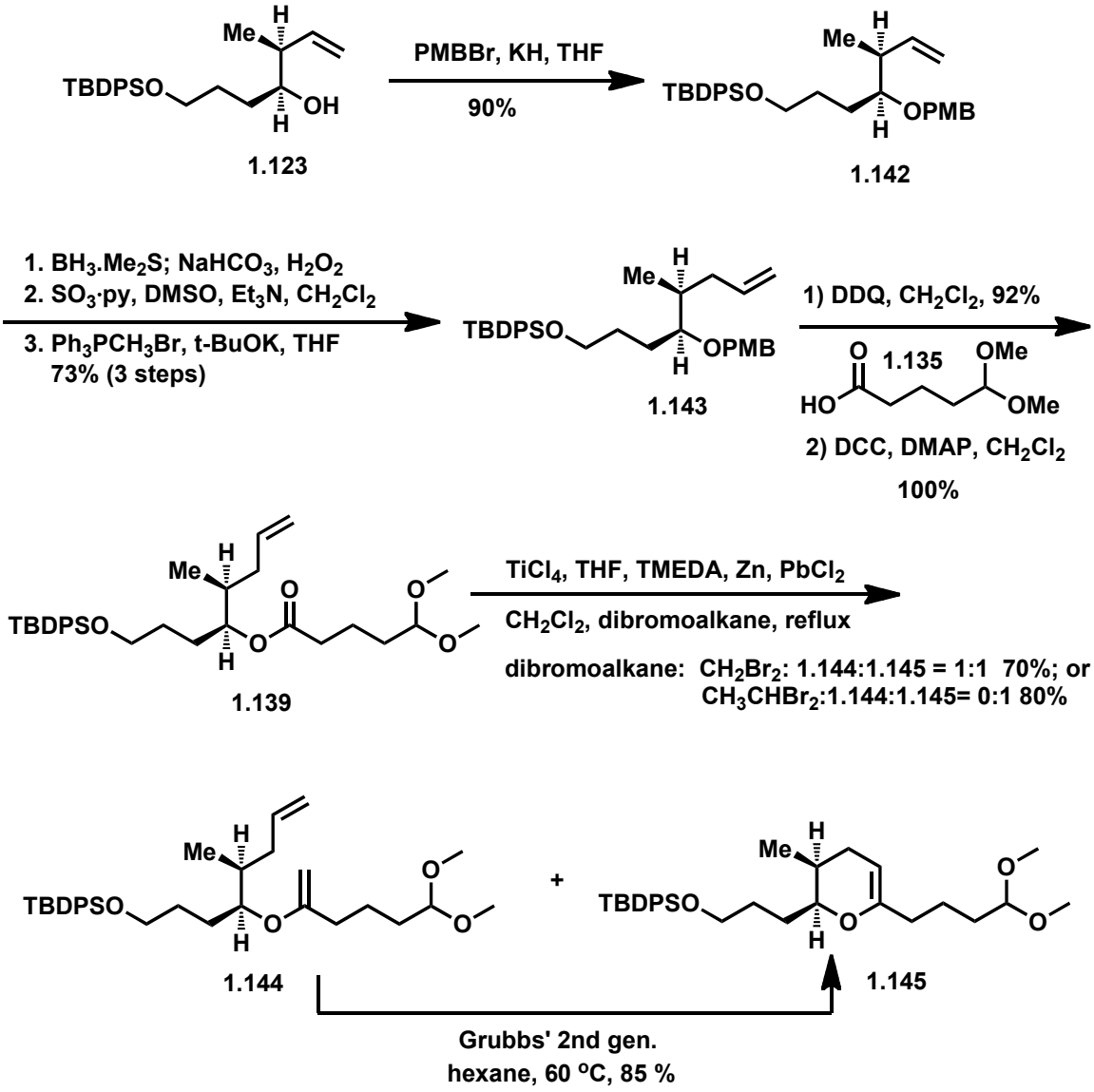
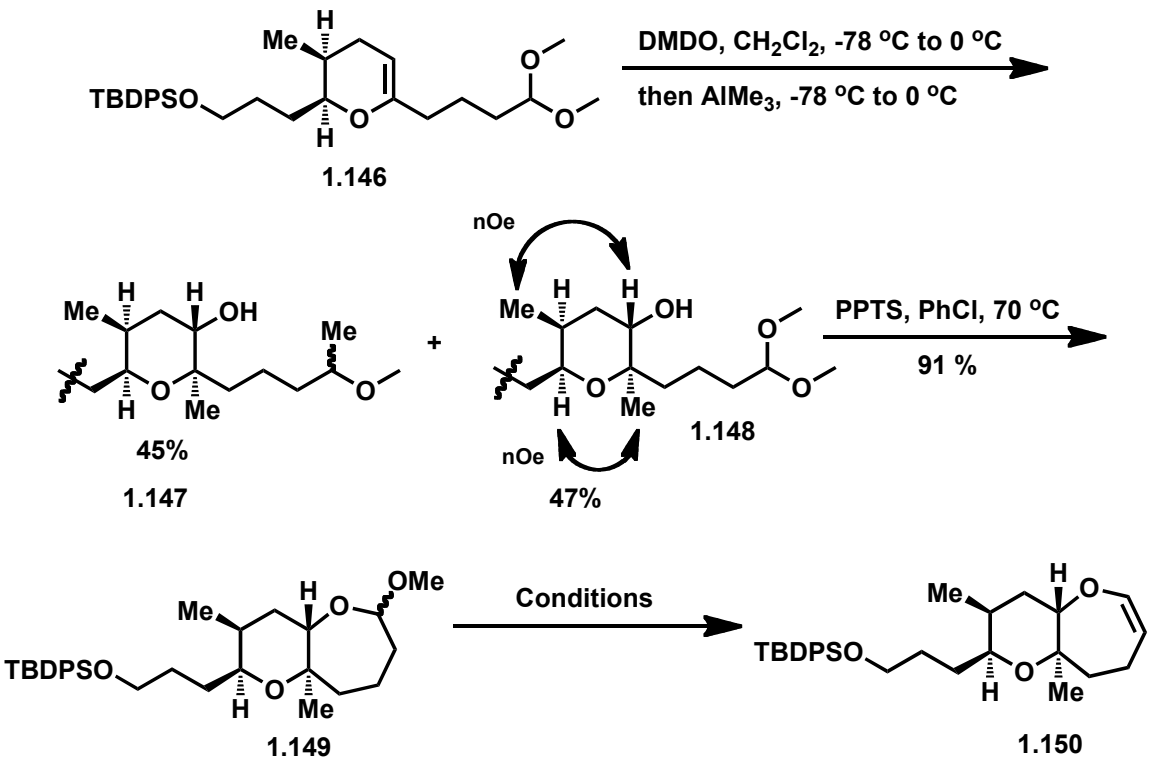


Figure 1.31. Synthesis of **1.139** and its conversion to cyclic enol ether **1.145**

Our initial investigation of the conversion of olefinic ester **1.139** to cyclic enol ether **1.145** employed the reduced titanium reagent derived from dibromomethane and resulted in the formation of a 1:1 mixture of cyclic enol ether **1.144** and acyclic enol ether **1.145** in 70% yield.[77] The acyclic enol ether could be transformed into cyclic material by subjection to Grubbs' second generation catalyst.[77]

During his work, Dr. Karthik Iyer found that a difference in the product distribution (acyclic vs. cyclic enol ether) could be controlled by using dibromoethane as the dibromoalkane source.[73] The fact that cyclic material could be generated exclusively by utilizing a more substituted titanium alkylidene reagent was unprecedented. Our group has subsequently investigated the scope of the reaction and has found it to be broad.[73] As part of this scope, we took olefinic-ester **1.139** and subjected it to the titanium ethylidene reagent. It was found that the reaction afforded the cyclic enol ether exclusively in 80% yield (Refer to chapter 2 for a more detailed discussion of olefinic-ester cyclizations). We next converted the enol ether **1.146** to the secondary alcohol **1.147** by utilizing our previously established method involving DMDO and $AlMe_3$ to generate α-*C*-glycosides (Figure 1.32).[76] Unfortunately, this strategy was unsuccessful and led to decomposition of the epoxide. To circumvent the problem, enol ether **1.146** was subjected to reaction with "acetone free" DMDO in CH_2Cl_2 at 0 ^{0}C to form the epoxide that was then directly subjected to $AlMe_3$, without concentration, to provide the product as a single diastereomer in moderate yield. Although this modification of our protocol delivered the desired product **1.148**, a significant amount of byproduct (35-55%) in which $AlMe_3$ addition occurred to the acetal was obtained.A number of conditions have been explored to avoid the formation of **1.147**.



Entry	Conditions	Yield of 1.150
1	PPTS, Py, PhCl, 140 °C	24 %
2	$BF_3{\cdot}OEt_2$, DIPEA, CH_2Cl_2 -78 °C to rt	N.R.
3	$Sc(OTf)_3$, Et_3N, CH_2Cl_2, -78 °C to rt	dec.
4	TMSOTf, DIPEA, CH_2Cl_2 -78 °C to rt	90%
5	TBSOTf, DIPEA, CH_2Cl_2 -78 °C to rt	N.R.
6	$SnCl_4$, DIPEA, CH_2Cl_2 -78 °C to rt	N.R.
7	TMSCl, NaI, CH_3CN, 0 °C to rt	dec.

Figure 1.32. Epoxidation/$AlMe_3$ addition and optimization of mixed acetal elimation.

Different methyl nucleophiles and additives including sacrificial acetals and solvent screens were also carried out to no avail. The substrate was then modified to incorporate more hindered acetals in hopes of preventing $AlMe_3$ coordination. Regardless of the nature of the acetal, the generation of the methyl adduct was still problematic. Different non-acetal groups such as silyl ethers and benzyl ethers were also investigated. These substrates delivered the product in low yields with various side products.

Subjection of **1.148** to PPTS in chlorobenzene at 70 ºC affected cyclization to give mixed cyclic acetal **1.149** in 91% yield. Next, mixed acetal **1.149** was subjected to PPTS, pyridine and heat to promote elimination to give the desired bicyclic enol ether in 24% yield. In contrast to previous efforts, when we attempted the direct conversion from **1.148** to **1.150**, it led to decomposition. The low yields can be attributed to the mixed acetal's instability to elevated temperatures. When the mixed acetal was subjected to the same conditions using lower temperatures, starting material was isolated. To overcome this problem, we investigated a variety of Lewis acid mediated elimination conditions and it was found that TMSOTf and excess of iPr$_2$NEt lead to the formation of **1.150** in high yield. chloride at -78 ^{0}C ketone **1.152** was isolated exclusively. The resultant ketone is formed from a pinacol rearrangement that is speculated to be promoted by Lewis acidic magnesium salts from the Grignard reagent. After much experimentation, allyl addition was successful when the temperature of the Grignard addition was raised to 0 ^{0}C. The product **1.153** was obtained as a single diasterisomer in 82% yield. The ketone side product was still observed although to much lesser extent than when the addition was carried out at lower temperatures.Next, with oxepene **1.150** in hand, we investigated α-*C*-glycoside formation (Figure 1.33).

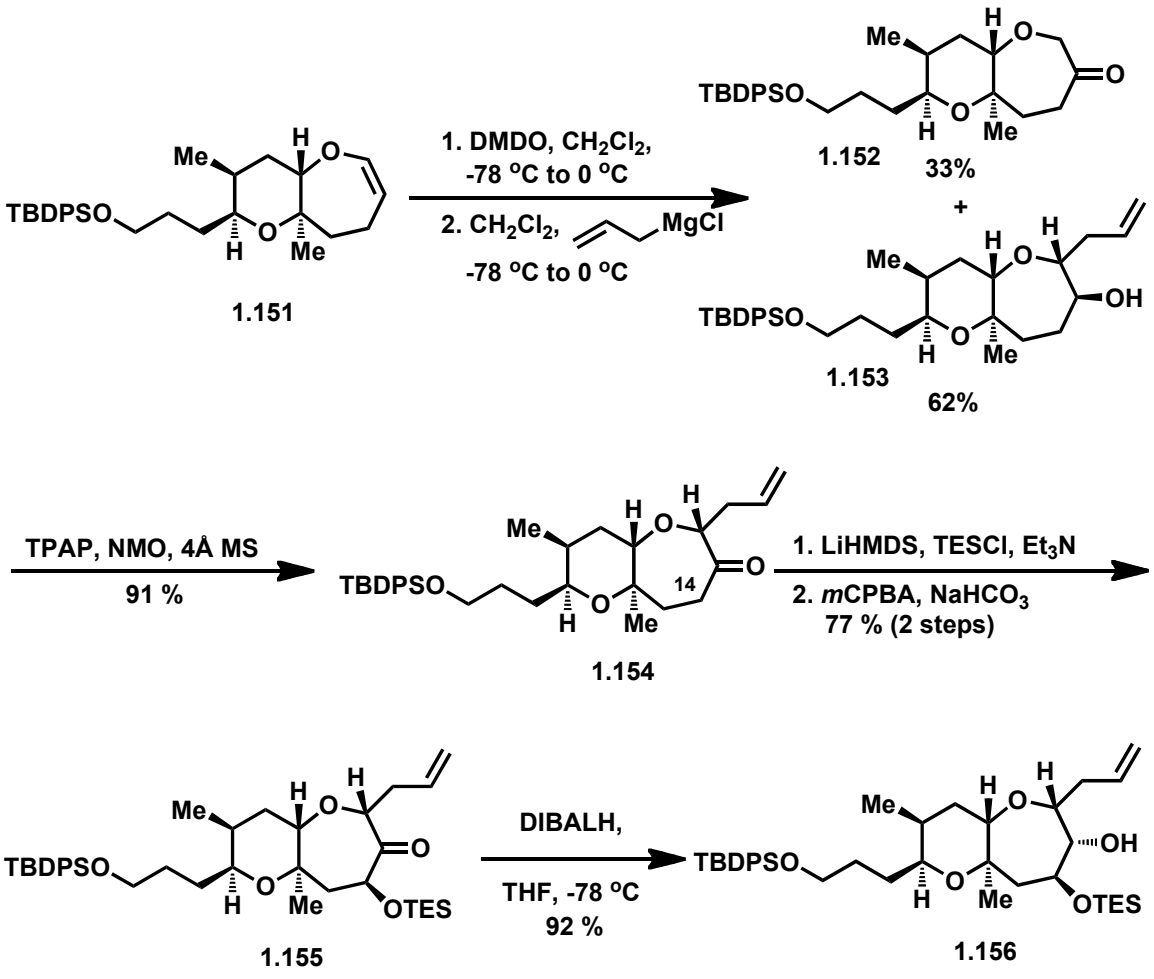


Figure 1.33. Synthesis of the C14-C15 *anti* diol **1.156**.

When **1.150** was initially subjected to DMDO and allyl magnesium chloride.

To convert compound **1.153** to the desired coupling precursor **1.114**, the C14 hydroxyl group needed to be installed. To do this, the secondary alcohol present in **1.153** was oxidized using TPAP/NMO in the presence of 4Å molecular sieves to give the ketone **1.154** in 91% yield.[43] The use of the Dess-Martin periodinane to oxidize **1.153** gave comparable yields.[78]

The ketone **1.154** was then subjected to a Rubottom oxidation sequence to give **1.155** in 77% yield over two steps.[79] Reduction of the ketone to form the desired 1,2-*syn* diol was attempted. However, *i*BuAlH reduction of the TES-protected hydroxyketone led exclusively to the undesired C14-C15 *anti* diol **1.156**.[77]

When the TES ether **1.155** was removed (CSA, MeOH:CH_2Cl_2, 90 %) and the resulting hydroxy ketone **1.157** was subjected to reductive conditions (*i*BuAlH, THF, -78 ^{0}C) the reduction was found to give the C14-C15 *syn* diol **1.159** suggesting the importance of the free hydroxy group (Figure 1.34). This is similar to the results obtained by Sasaki as was shown in Figure 1.12.[28] The stereochemical rationale for this result is as follows: Initially, the C14 hydroxy group is deprotonated with *i*BuAlH to form the corresponding aluminum alkoxide. Coordination to the adjacent C15 ketone gave the five-membered metallocycle **1.158**, thereby blocking the β-side of the molecule and forcing the second equivalent of the reductant to approach from the less hindered α-side. The diol was obtained as a 10:1 mixture of diastereoisomers favoring the *syn* product. The two diastereoisomers could be separated by flash chromatography. The stereochemistry at the newly formed C14 and C15 positions were confirmed by nOe analysis of the acetonide **1.161** (Figure 1.35)

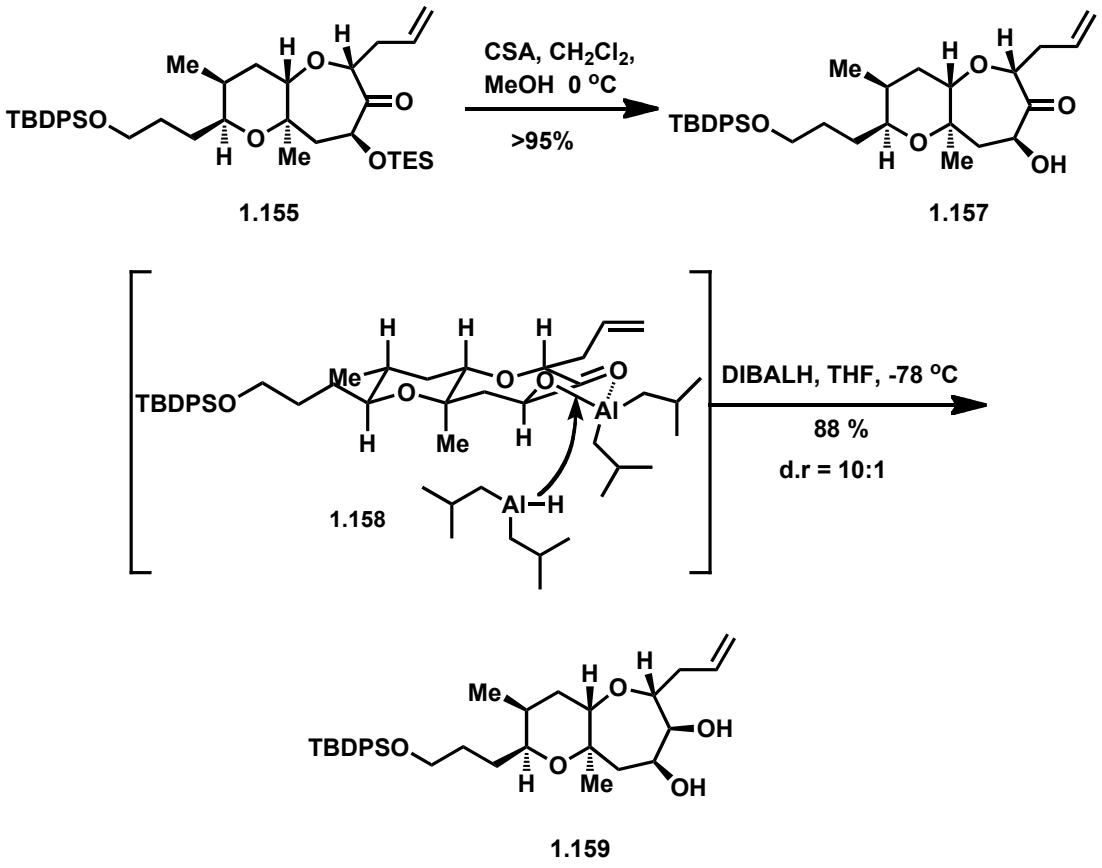


Figure 1.34 Synthesis of the C14-C15 *syn* diol **1.159**.

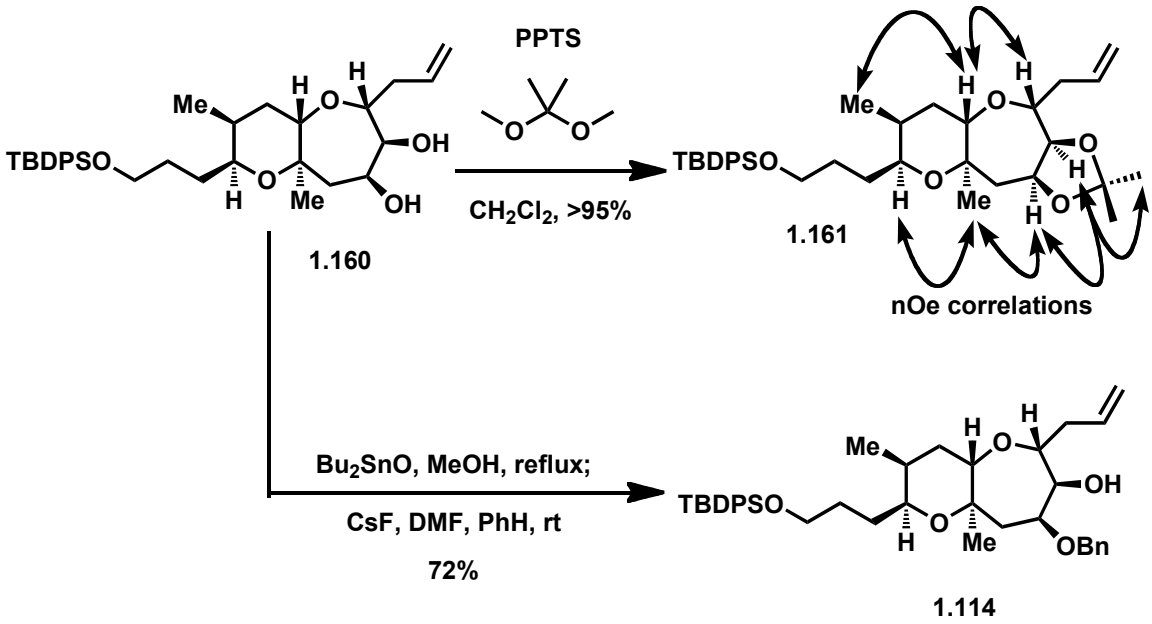


Figure 1.35. nOe correlations of acetonide **1.161** and monobenzylation of **1.150**.

To complete the synthesis of the coupling precursor, selective benzylation of the C14 hydroxyl group was achieved using the stannane complex derived from dibutyltinoxide and its subjection to CsF and benzyl bromide to provide exclusive formation of the C14 benzyl ether **1.114** in 72 % yield. Starting material could also be recovered in 23% yield.

Our synthesis of the E ring acid commenced with (*S*)-2,3-*O*-isopropylidene glyceraldehyde **1.162** (Figure 1.36).[80] In four steps, the olefinic ester **1.163** could be made in gram quantities. Subjection of **1.163** to the titanium ethylidene reagent affected cyclization to give the desired oxepene **1.164** in 72% yield. Oxidation of the enol ether with DMDO followed by *i*BuAlH reduction provided the secondary alcohol which was oxidized to the corresponding ketone **1.165** with TPAP/NMO in 80% overall yield. Methyl addition to the ketone using methyl magnesium bromide provided the C26 tertiary alcohol **1.166** as a 6:1 mixture of diasterisomers favoring the desired compound. In an additional 5 steps, **1.166** was converted to the terminal olefin **1.167**. To make the carboxylic acid, the olefin **1.168** was dihydroxylated and the resultant diol was oxidatively cleaved to give an aldehyde. Pinnick oxidation provided the E ring coupling subunit **1.169**.

With the requisite fragments in hand, Dr. Jie Zhou set out to assemble the pentacyclic polyether core (Figure 1.37).[81] Esterification of the coupling subunits was carried out using Yamaguchi's protocol to afford the ester in 80% yield. The newly formed olefinic-ester **1.170** was subjected to the titanium ethylidene reagent to smoothly produce enol ether **1.171** in 72% yield. To complete the D ring the angular C19 methyl had to be installed. The first of several conditions used were a DMDO epoxidation

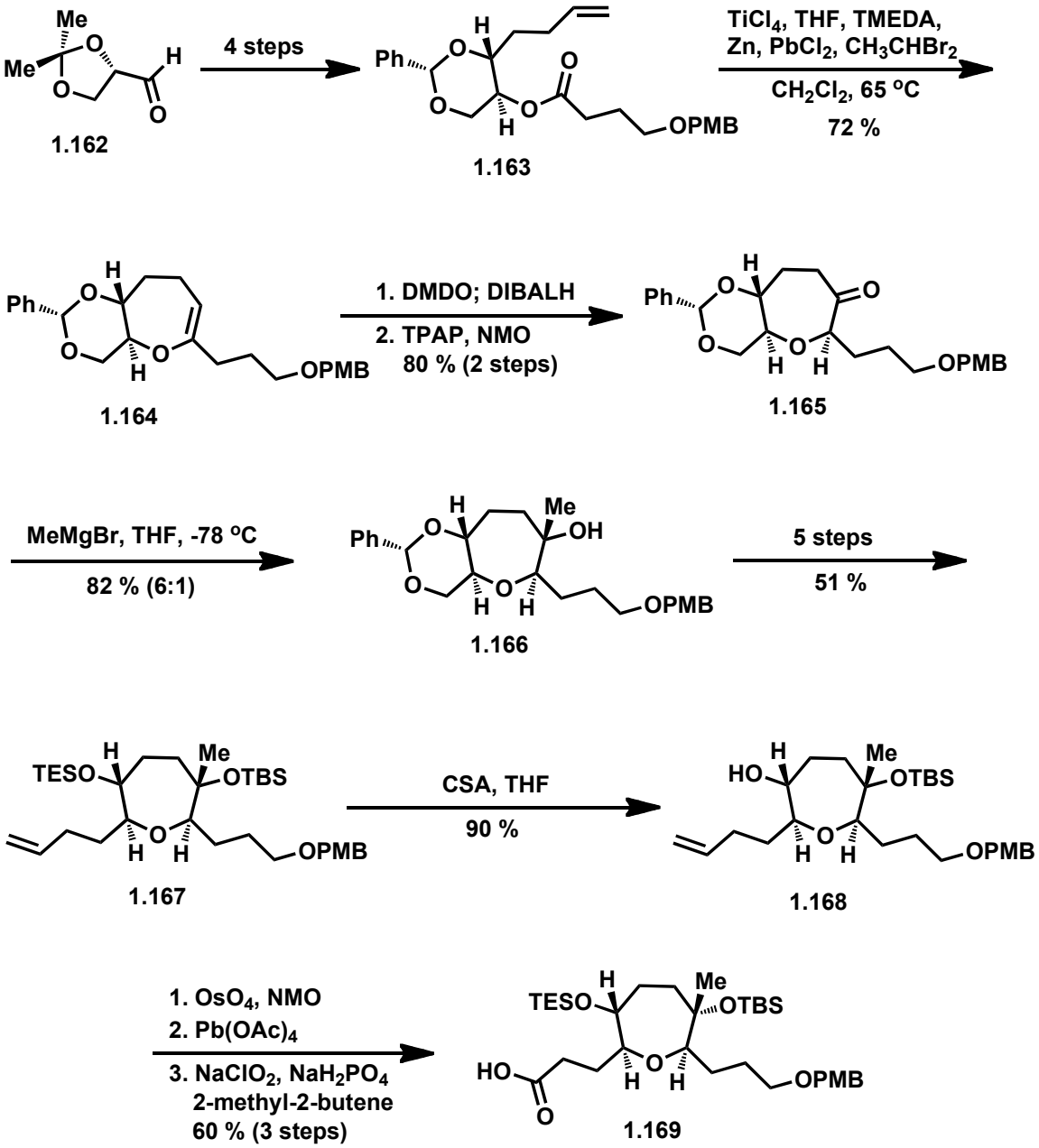


Figure 1.36 Construction of the E ring fragment.

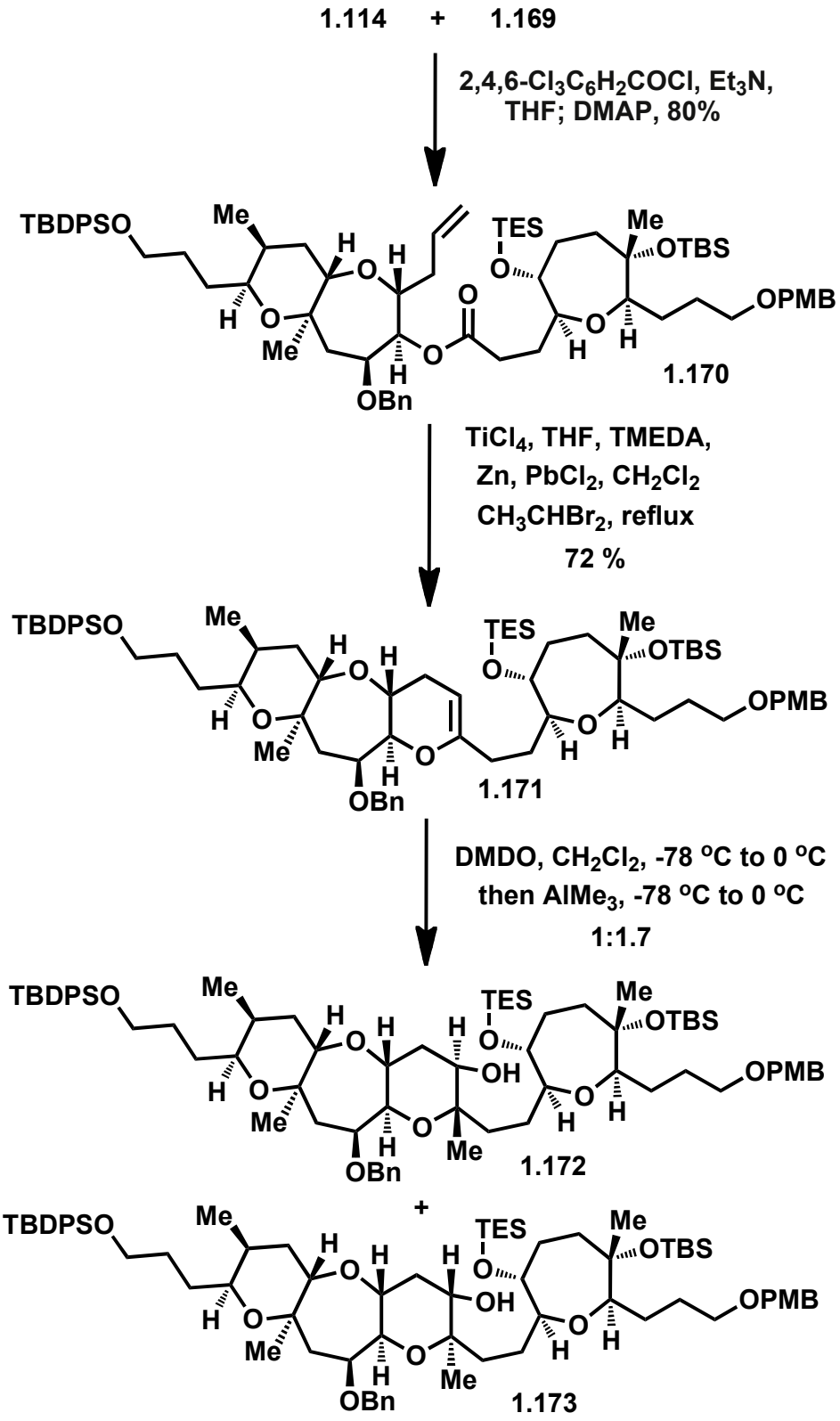


Figure 1.37 Formation of the C ring and attempted installation of the C19 methyl

followed by $AlMe_3$ addition. These conditions, however gave a 1:1.7 mixture of diastereoisomers **1.172** and **1.173** due to the lack of selectivity during the epoxidation step. Conditions developed by Dr. Jie Zhou that employ the use of DMDO/ $ZnMe_2$ and TBSOTf were also explored. These conditions are known for generating axial addition products regardless of the epoxidation selectivity. When Dr. Zhou employed these conditions it was found that they gave irreproducible results that ultimately forced us to consider a different approach to synthesize the core.

Second Generation Approach to Brevenal

In order to circumvent the lack of selectivity from the previously described DMDO epoxidation/$AlMe_3$ addition it was thought that the C19 methyl could be installed via a hydroxy ketone cyclization/methyl addition from the D ring enol ether **1.175** as shown in Figure 1.38. Here, we planned to use an olefinic ester cyclization from **1.176** to construct the D ring enol ether. Disconnection of the ester leads to the AB ring acid **1.177** and E ring olefin **1.178**.

The AB ring coupling precursor **1.177** was formed in four steps from intermediate **1.160**, which involved bis-TES protection, dihydroxylation, oxidative cleavage and Pinnick oxidation (Figure 1.39). The E ring olefin **1.178** bearing the benzyl ether was made from the corresponding olefinic ester as previously described in Figure 1.36. With both coupling partners in hand, fellow graduate student, Yuan Zhang began to investigate their coupling.

The esterification of E ring acid **1.178** and AB alcohol **1.177** using Yamaguchi's protocol produced moderate yields and we were unable to recover starting material

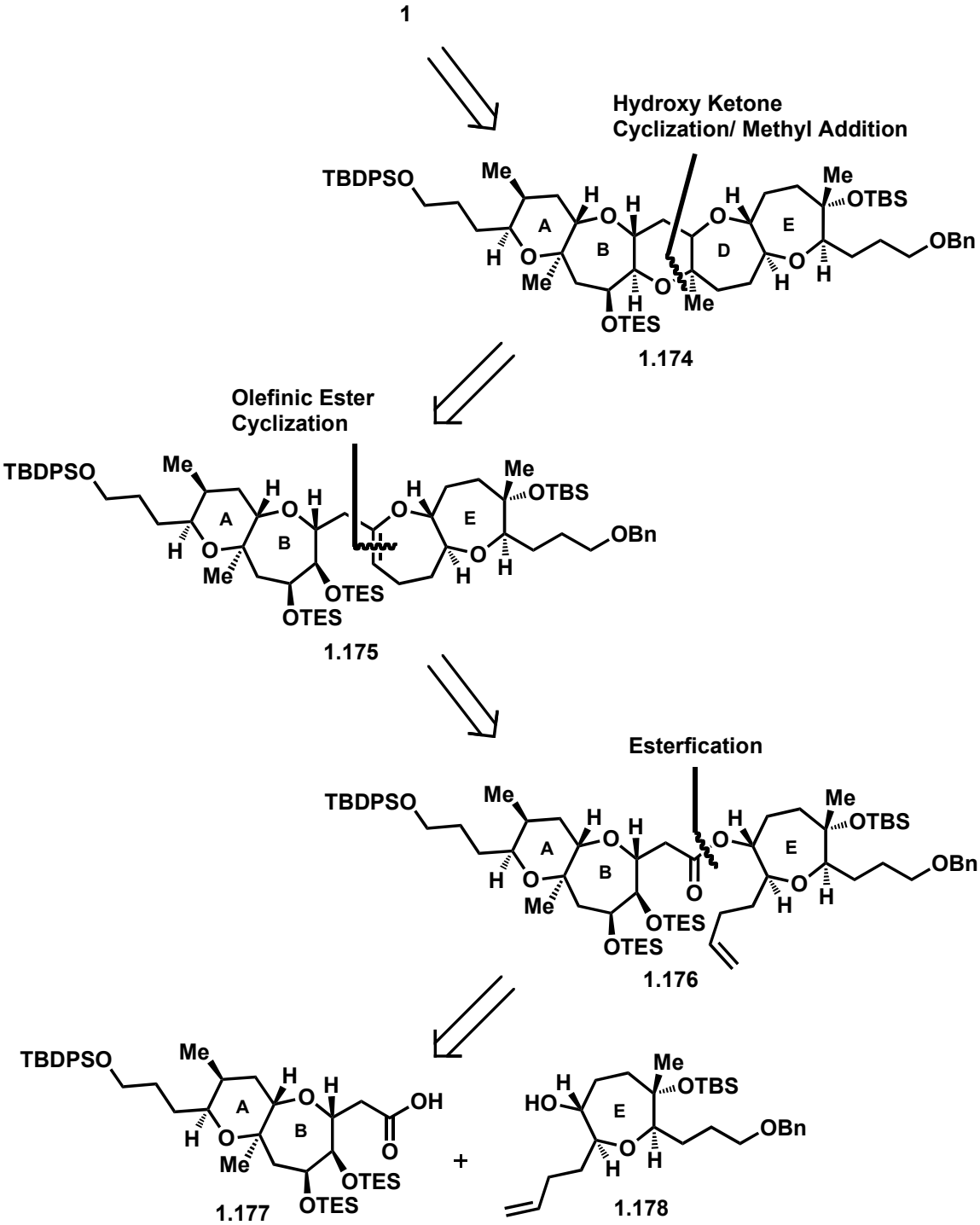
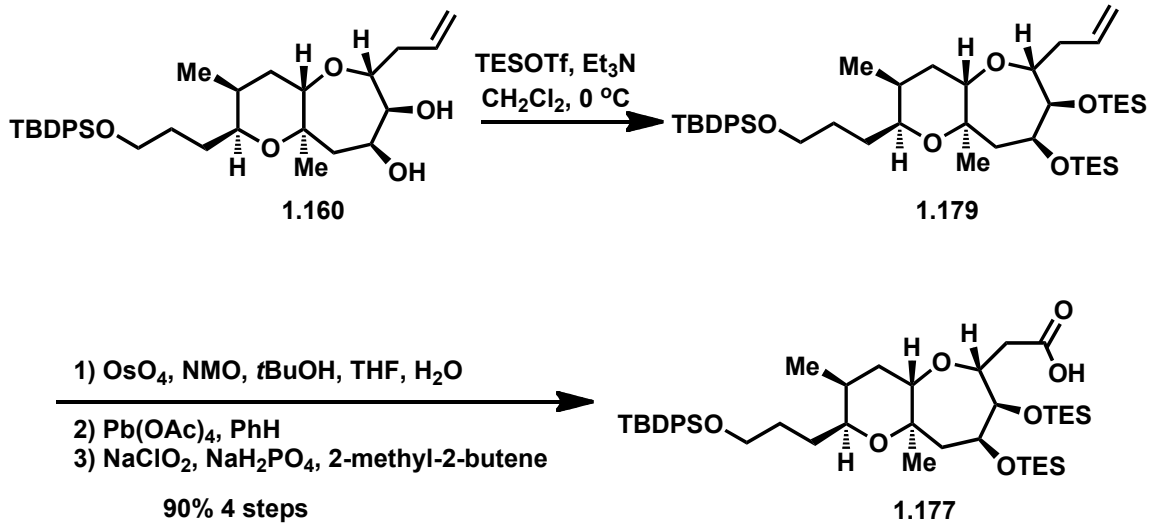


Figure 1.38. Second generation retrosynthesis of brevenal.



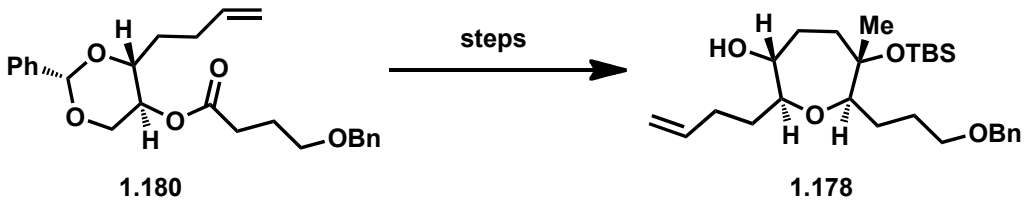


Figure 1.39. Synthesis of the requisite coupling fragments.

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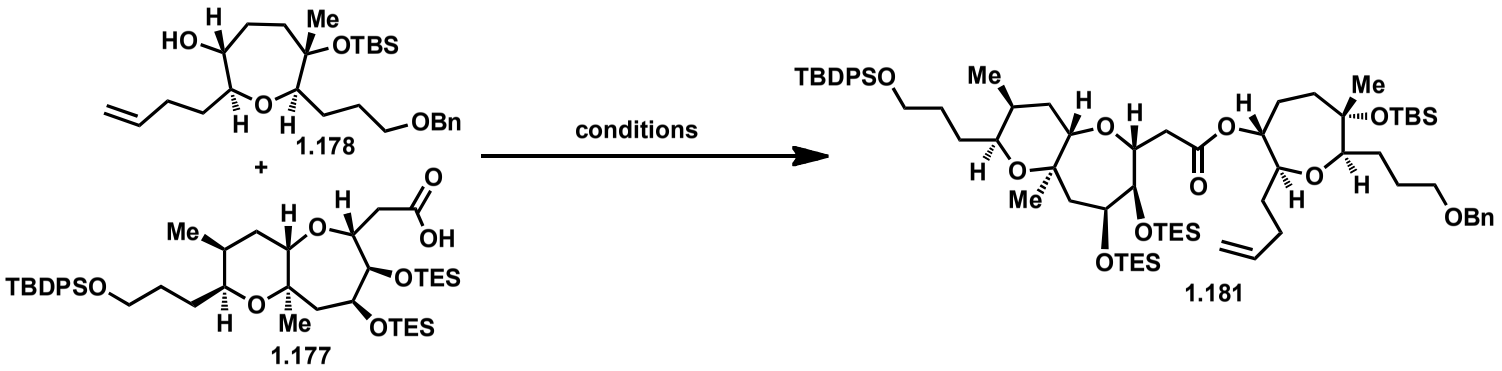
Figure (1.40).[38] We then turned to Shiina's protocol to affect ester formation and were delighted to isolate ester **1.181** in 87% yield under these conditions.[82]

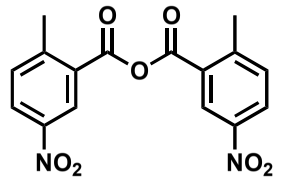
Next, olefinic ester cyclization using our titanium ethylidene reagent provided the D ring enol ether **1.182** with concomitant formation of acyclic enol ether **1.183** (Figure 1.41). The acyclic material **1.183** could be transformed into cyclic enol ether **1.182** by treatment with Grubbs' second generation catalyst. The next step was the installation of the ketone that was necessary for the formation of the C ring. This was accomplished by using a DMDO epoxidation/iBu$_2$AlH reduction sequence to give the secondary alcohol as a single stereoisomer. The secondary alcohol was oxidized with TPAP/NMO to give the ketone **1.184** in 65% from **1.182**.[43] During the formation of the thioacetal from **1.184** the C14 and C15 TES ethers were removed which induced cyclization to give a mixed thiol ketal. The free C14 hydroxyl group was protected as the TBS ether **1.185**. Installation of the angular methyl and construction of the pentacyclic core of brevenal occurred uneventfully when **1.185** was treated with $ZnMe_2$ and $Zn(OTf)_2$. The spectral data for structure **1.186**, a synthetic intermediate in both Sasaki's and Kadota's syntheses, matched their reported ^{1}H and ^{13}C NMR data.[28,53] Our total synthesis of brevenal was completed using a modification of Yamamoto and Kadota's end game protocol for the incorporation of the side chains.[28,53] The ^{1}H and ^{13}C NMR spectra of our synthetic **1.1** were in accordance with those of the naturally obtained material.

The key features of our synthesis include a convergent assembly of the pentacyclic polyether skeleton through an esterification reaction and the use of our olefinic ester metathesis strategy to generate the A, D and E rings of brevenal. Through the collaboration with Tom Murray, the material generated will serve to aid the



Entry	Conditions	Yield of 1.181
1	2,4,6-$Cl_3C_6H_2COCl$, Et_3N, THF; DMAP, 40°C	50%
2	MNBA, DMAP, CH_2Cl_2	87%

MNBA =



2-methyl-5-nitrobenzoic anhydride

Figure 1.40. Screening of different esterification conditions

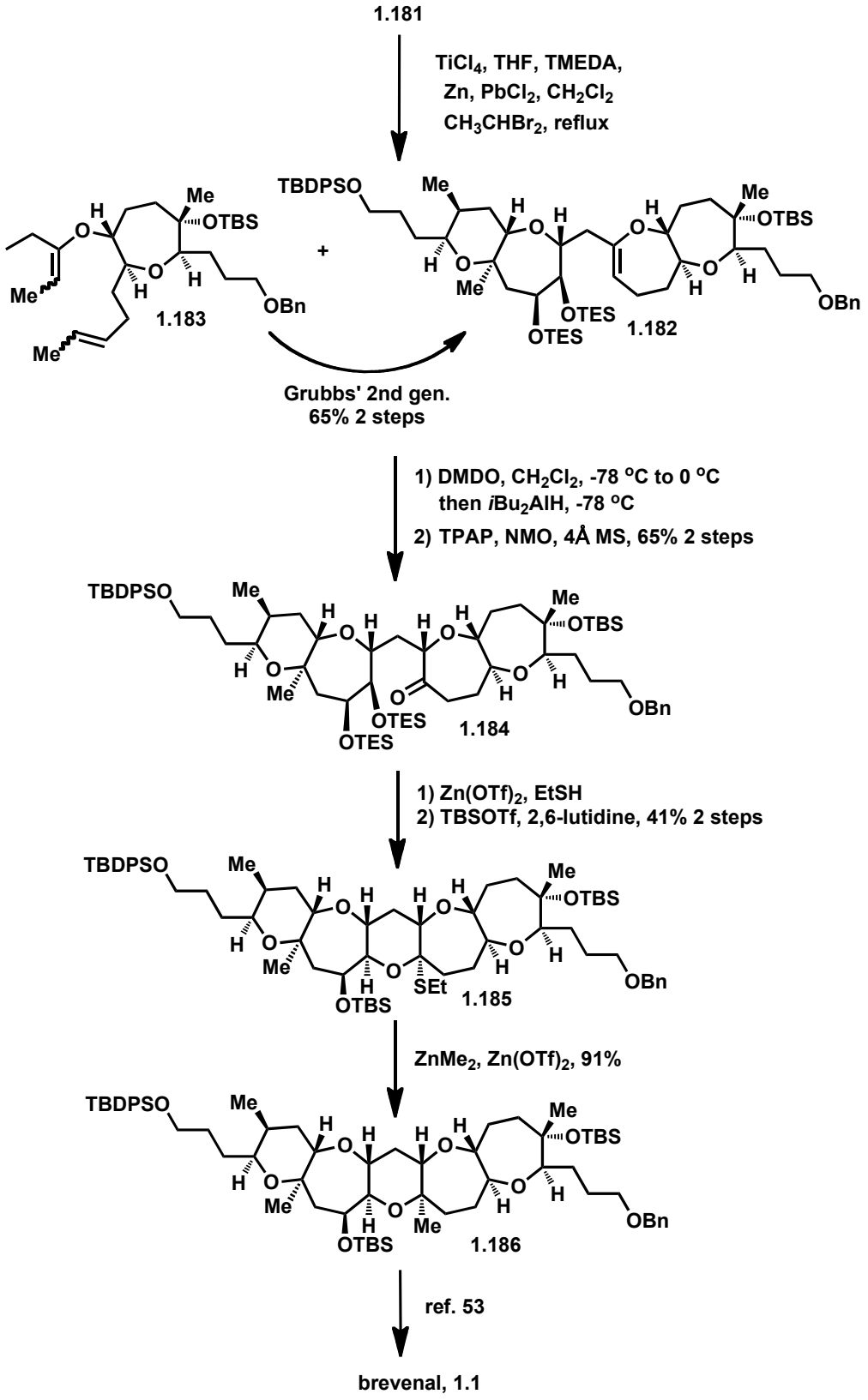


Figure 1.41. Synthesis of the pentacyclic core and completion of brevenal.

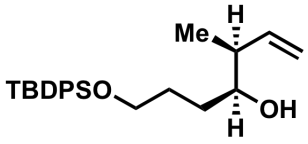
understanding of brevenal's biological properties. This study demonstrates the important role of total synthesis in the study of complex, biologically active natural products. Moreover, the highly convergent nature of the present synthesis will allow the synthesis of structural analogues for a more detailed structure-activity relationship studies of this intriguing natural product.

Supporting Information

General Experimental Procedures

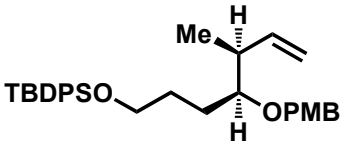
Unless otherwise noted, all reactions were performed under a nitrogen atmosphere in flame-dried glassware. NMR spectra were recorded on a Varian VXR-500 MHz spectrometer. Chemical shifts were reported in δ, parts per million (ppm), relative to benzene (7.16), dichloromethane (5.32) or chloroform (7.27) as internal standards. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. Dichloromethane, TMEDA and pyridine were dried by distillation from calcium hydride and saturated with nitrogen. Tetrahydrofuran and diethyl ether were dried from the sodium ketyl of benzophenone and distilled before use. Zinc dust (<10 μm, Aldrich) was activated by washing with 5% hydrochloric acid, H_2O, ether, and acetone and dried *in vacuo* overnight. The activated zinc was stored under nitrogen in a dessicator. All other reagents were used without further purification unless otherwise noted. Analytical thin–layer chromatography (TLC) was performed on silica gel plates (0.25 mm) precoated

with a fluorescent indicator. Flash chromatography was performed using 40–63 μm silica gel (200 X 400 mesh).



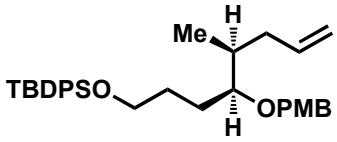
(3*S*,4*S*)-7-(*tert*-butyldiphenylsilyloxy)-3-methylhept-1-en-4-ol 1.123. A flame dried 3-neck 3.0 L flask equipped with an internal thermometer was charged with potassium *tert*-butoxide (33.80 g, 301.3 mmol and THF (205.0 mL). The slurry was cooled to -78 ^{o}C and *cis*-2-butene (56.00 mL, 625 mmol) was added followed by the dropwise addition of *n*-butyllithium (120.5 mL of a 2.5 M soln. in THF, 301 mmol). During the addition of *n*-butyllithium the temperature was maintained below -70 ^{o}C. After complete addition of *n*-butyllithium, the mixture was stirred at -45 ^{o}C for 12 min. The resulting solution was recooled to -78 ^{o}C, and to it was added dropwise (+)-*β*-methoxydiisopinocamphenyl borane (361 ml of a 1 M solution in Et_2O, 361 mmol) and the temperature was maintained below -70 ^{o}C. The reaction mixture was stirred at -78 ^{o}C for 30 min and boron trifluoride etherate (50.9 mL, 400 mmol) was added dropwise. Then neat aldehyde **1.122** (82.0 g, 251 mmol) was added dropwise at -78 ^{O}C. The reaction mixture was stirred at -78 ^{o}C for 3 h at which point aq. NaOH (376 ml of a 3.0 M aq. solution, 1004 mmol) followed by aq. H_2O_2 (160 ml of a 30 % solution). The reaction mixture was warmed to rt for 1 h and then diluted with hexanes (500 ml). The organic phase was washed with H_2O (2 X 30 ml), dried (Na_2SO_4) and concentrated. The resulting residue was distilled (145 ^{o}C, 0.01 torr) to remove pineol. Flash chromatography of the resulting residue (hexanes/EtOAc 100:1 to 10:1) yielded alcohol **1.123** (86.1 g, 90%, 95:5 er) as a colorless oil whose spectroscopic details were in accordance with that previously

reported[77]: R_f 0.35 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.81-7.76 (m, 4 H), 7.27-7.22 (m, 6 H), 5.70 (ddd, *J* = 17.1, 10.7, 7.8 Hz, 1 H), 5.01-4.95 (m, 2 H), 3.7-3.62 (m, 2 H), 3.34-3.26 (m, 1 H), 2.10 (dddd, *J* = 13.7, 6.8, 6.8, 6.8 Hz, 1 H), 1.77-1.68 (m, 1 H), 1.62-150 (m, 2 H), 1.38-1.28 (m, 1 H), 1.18 (s, 9 H), 1.00 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 142.2, 136.4, 134.6, 130.3, 128.4, 115.0, 74.9, 64.9, 44.7, 31.8, 29.9, 27.5, 19.8, 15.3.



***t*-butyl-(4*S*,5*S*)-4-4-methoxybenzyl-5-methylhept-6-en-1-yl diphenylsilane 1.142.** To a solution of alcohol **1.123** (60.1 g, 158 mmol) in THF (250 ml) at rt was added KH (26.2 g, 196 mmol) as a 30% dispersion in mineral oil. The reaction mixture was allowed to stir for 20 min. at which point the color of the reaction mixture appeared yellow. PMB-Br (39.0 g, 196 mmol) was added over 20 min. After 12 h the reaction was quenched with sat. NH_4Cl (aq., 100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes:ethyl acetates, 50:1 to 20:1 to 10:1) gave **1.142** (69.1 g, 90%) R_f 0.40 (20:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = +14.7° (c = 1.6, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.79 (m, 4H), 7.25 (m, 8H), 6.82 (d, *J* = 8.3 Hz, 2H) 5.88 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.03 (m, 2H), 4.36 (s, 2H), 3.69 (m, 2H), 3.32 (s, 3H), 3.17 (m, 1H), 2.44 (m, 1H), 1.83-1.50 (m, 4H), 1.94 (s, 9H), 1.07 (d, *J* = 6.84 Hz, 1H). ^{13}C NMR (125 MHz, C_6D_6) δ 160.0, 142.0, 136.4, 134.9, 132.1, 130.4, 129.7, 128.7, 128.5, 114.6, 114.5, 82.8, 71.8, 64.9, 55.2, 41.6, 29.3, 28.0. 27.6, 19.8, 16.3; DEPT (125 MHz, C_6D_6) δ CH_3: 55.2, 27.6, 16.3, CH_2 114.6, 71.8, 64.9, 29.3, 28.0 CH: 142.0, 136.4, 130.4, 129.7, 128.7, 128.5; IR (film) 2918, 2850, 1613, 1455, 1427,

1248, 1084 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{32}H_{42}O_3SiNa$ 525.28 ($M+Na^+$), found 525.3.

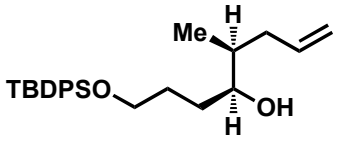


***t*-butyl(((4*S*,5*S*)-4-((4-methoxybenzyl)oxy)-5-methyloct-7-en-1-yl)oxy) diphenylsilane 1.143.** To a solution of alkene **1.142** (38.0 g, 77.75 mmol) in THF (1.5 L) at -10 ^oC was added BH_3-DMS (62.0 ml, 10.0 M in THF). The reaction mixture was stirred at this temperature for 5 h and then warmed to rt and stirred for an additional 2 h. The reaction mixture was recooled to 0 ^oC at which point aq. NaOH (300 mL 3.0 M) was slowly added followed by H_2O_2 (aq. 30%, 101 mL). The reaction mixture was allowed to stir at rt for 12 h. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The extracts were combined, dried (Na_2SO_4), and concentrated. The resulting residue was passed through a plug of silica (hexanes:ethyl acetates, 1:1) to give the corresponding primary alcohol which was carried on to the oxidation step without additional purification. R_f 0.30 (1:1 hexanes/EtOAc); Crude spectroscopic data: ^1H NMR (500 MHz, C_6D_6) δ 7.79 (m, 4H), 7.24-7.22 (m, 8H), 6.80 (d, *J* = 8.8 Hz, 1H), 4.33 (ABq, *J* = 11.24 Hz, 2H), 4.22 (bs, 1H), 3.72-3.65 (m, 2H), 3.56 (ddd, *J* = 10.9, 5.5, 5.4 Hz, 1H), 3.46 (m, 2H), 3.31 (s, 3H), 3.16 (m, 1H), 1.89 (m, 1H), 1.83-1.52 (m, 7H), 1.94 (s, 9H), 0.85 (d, *J* = 6.84 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 160.0, 136.4, 130.3, 129.9, 114.4, 83.3, 71.7, 64.7, 61.7, 55.1, 36.2, 34.9, 30.1, 27.8, 27.5, 27.1, 26.8, 16.6. IR (film) 3416, 2919, 2848, 1632, 1427 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{32}H_{44}O_4SiNa$ 543.29 ($M+Na^+$), found 543.3.

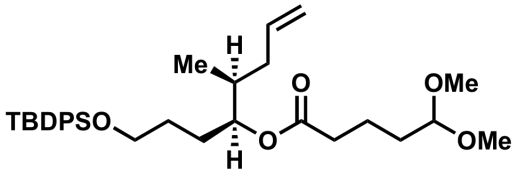
To a solution of the crude primary alcohol from above (20.0 g, 38.4 mmol) in CH_2Cl_2 (350 ml) was added Dess-Martin periodinane (18.0 g, 42.24 mmol) at rt. The reaction was stirred at this temperature for 4 h at which point aq $Na_2S_2O_3$ (192 mL, 2.0

M) and sat. $NaHCO_3$ (aq., 100 mL) was added and allowed to stir for 30 min. The reaction mixture was diluted with Et_2O (100 ml). The organic phase was separated, dried (Na_2SO_4) and concentrated to afford the crude aldehyde, which was carried on to the Wittig reaction without additional purification.

The crude aldehyde (42.24 mmol) from above was diluted in THF (350 ml) and the Wittig reagent (73 mmol, prep. according to the procedure below) was then added slowly. After 2 h the reaction was quenched with sat. NH_4Cl (aq., 100 ml) and extracted with CH_2Cl_2 (3 X 50 ml). The extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (hexane/EtOAc 20:1) yielded alkene **1.143** (29.3 g, 73 % over three steps) as a colorless oil. The Wittig reagent was prepared as follows: to methyltriphenyl phosphonium bromide (27.4 g, 76.8 mmol) in THF (200 ml) at rt was added a solution of potassium *tert*-butoxide (73.0 ml of a 1 M soln. in THF) dropwise. The resulting yellow solution was used as described above after stirring for 1 h. R*f* 0.75 (10:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = +7.6 (c = 1.9, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.80 (m, 4H), 7.24 (m, 6H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.77 (dddd, *J* = 17.1, 10.2, 7.0, 7.0 Hz, 1H), 5.07-5.02 (m, 2H), 4.36 (ABq, *J* = 11.72 Hz, 2H), 3.70 (m, 2H), 3.31 (s, 3H), 3.21 (dt, *J* = 8.8, 4.9 Hz, 1H), 2.36 (ddd, *J* = 13.4, 6.6, 5.1 Hz, 1H), 1.94 (m, 1H), 1.76-1.55 (m, 5H), 1.20 (s, 9H), 0.96 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.7, 160.0, 138.6, 136.4, 134.8, 134.8, 132.3, 130.3, 129.7, 128.7, 128.4, 116.2, 114.4, 82.4, 71.8, 64.8, 55.1, 38.0, 36.4, 29.8, 27.5, 27.4, 19.8, 15.2; DEPT (125 MHz, C_6D_6) δ CH_3: 55.1, 27.5, 15.2 CH_2: 71.8, 64.8, 38.0, 29.8, 27.4 CH: 138.6, 136.4, 130.3, 129.7, 128.7, 128.4, 1162, 114.4; ESI/MS (*m/z*) calcd for $C_{33}H_{44}O_3SiNa$ ($M+Na^+$) 539.30, found 539.3.

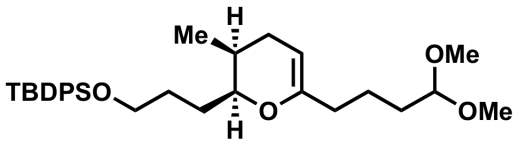


(4*S*,5*S*)-1-((tert-butyldiphenylsilyl)oxy)-5-methyloct-7-en-4-ol 1.144. To a solution of PMB ether **1.144** (21.0 g, 40.7 mmol) in CH_2Cl_2 (300 mL) and aq. pH 7 buffer solution (30 mL, 1.0 M) at rt was added DDQ (13.85 g, 61.0 mmol) in a single portion. The reaction mixture was allowed to stir for 1.5 h and was then quenched by addition of saturated aq. $NaHCO_3$ solution (50 mL). The phases were separated and the aqueous phase was extracted three times with CH_2Cl_2 (100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography (hexanes:ethyl acetates, 20:1 to 10:1 to 5:1) gave **1.144** (14.85 g, 92%) R_f 0.20 (10:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -3.30 ° (c = 1.55, THF); ^{1}H NMR (500 MHz, C_6D_6) δ 7.79-7.45 (m, 4 H), 7.25-7.21 (m, 6 H), 5.74 (dddd, *J* = 17.5, 10.8, 8.0 Hz, 1 H), 5.06-4.90 (m, 2 H), 3.64 (t, *J* = 5.8 Hz, 2 H), 3.40-3.33 (m, 1 H), 2.20 (ddd, *J* = 12.0, 6.0, Hz, 1 H), 1.89 (ddd, *J* = 14.8, 8.0 Hz, 1 H), 1.71-1.62 (m, 1 H), 1.57-1.49 (m, 1 H), 1.44-1.34 (m, 2 H), 1.17 (s, 9 H), 0.87 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 138.4, 136.4, 136.4, 134.6, 130.4, 128.4, 116.2, 74.3, 64.9, 39.1, 38.8, 31.9, 30.1, 27.4, 19.8, 14.0 DEPT (125 MHz, C_6D_6) δ CH_3: 27.4, 13.9 CH_2: 116.2, 64.9, 38.8, 31.9 CH: 138.4, 136.4, 136.4, 130.4, 128.4, 74.3, 39.1; IR (film) 3432, 2956, 2861, 1108 ESI/MS (*m/z*) calcd for $C_{25}H_{36}O_2SiNa$ ($M+Na^+$) 419.2, found 419.2



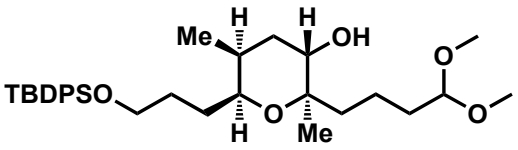
(4*S*,5*S*)-1-(*tert*-butyldiphenylsilyloxy)-5-methyloct-7-en-4-yl-5,5-dimethoxypent

anoate 1.136. To the alcohol (7.7 g, 21.6 mmol) in CH_2Cl_2 (100.0 ml) at rt was added the acid **1.123** (4.2 g in 10.0 ml CH_2Cl_2, 25.9 mmol), followed by 1,3 dicyclohexylcarbodiimide (13.33 g, 64.7 mmol), then DMAP (5.20 g, 43.1 mmol). The reaction mixture was stirred at rt for 12 h and then concentrated. Flash chromatography (100:1 hexane:EtOAc, then 20:1 hexane:EtOAc) gave 11.08 g (95% yield) of **1.136** as a colorless oil whose spectroscopic details were in accordance with that previously reported[77]: R_f 0.51 (5:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.82-7.77 (m, 4 H), 7.28-7.22 (m, 6 H), 5.71 (dddd, *J* = 17.1, 9.8, 7.3, 7.3 Hz, 1 H), 5.08 (ddd, *J* = 7.8, 3.9, 3.9 Hz, 1 H), 5.05 (d, *J* = 1.4 Hz, 0.5 H), 5.02 (bs, 1 H), 5.0 (bs, 0.5 H), 4.25 (t, *J* = 5.3 Hz, 1 H), 3.71-3.61 (m, 2 H), 3.11 (s, 6 H), 2.17 (t, *J* = 7.3 Hz, 2 H), 1.82 (ddd, *J* = 15.6, 8.3, 8.3 Hz, 1 H), 1.76-1.68 (m, 2 H), 1.67-1.52 (m, 8 H), 1.18 (s, 9 H), 0.89 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 173.0, 137.5, 136.4, 134.5, 130.3, 128.4, 116.8, 104.6, 76.4, 64.3, 52.63, 52.57, 38.4, 37.2, 34.6, 32.5, 29.6, 28.6, 27.5, 21.0, 19.8, 14.6.



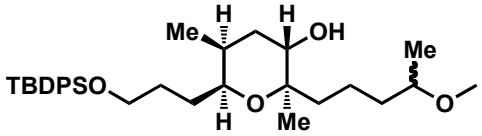
***tert*-butyl-(3-((2*S*,3*S*)-6-(4,4-dimethoxy-butyl)-3-methyl-3,4-dihydro-2*H*-pyran-2-yl) propoxy)diphenylsilane 1.145**. An oven dried two-necked flask fitted with a condenser was cooled to 0 °C and charged with CH_2Cl_2 (1320 ml) followed by $TiCl_4$ (32.0 ml, 56.0 mmol). To the resulting solution was added THF (155.6 ml, 1774 mmol) dropwise at which time the solution turned yellow. The addition of THF was followed by the dropwise addition of TMEDA (267.7 ml, 1774 mmol) resulting in the formation of a brown solution. The ice bath was removed and the mixture was allowed to stir for 20

min. Activated Zn dust (43.2 g, 665 mmol) and $PbCl_2$ (9.76 g, 35.1 mmol) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3-5 min. To the slurry was transferred a solution of ester **1.139** (10.0 g, 18.5 mmol) and CH_3CHBr_2 (26 ml, 295 mmol) in CH_2Cl_2 (127.0 ml + 127.0 ml rinse) via cannula. The reaction mixture was then heated to reflux for 2 h. Following this time period the mixture was cooled to 0 °C and quenched with sat K_2CO_3 (aq., 162 ml). After stirring for 30 min at 0 °C, the resulting mixture was filtered washing with 1:1 EtOAc (3 x 200 mL) and the filtrate was concentrated. The resulting residue was taken up in 100:1 hexanes:EtOAc and filtered through a plug of silica (100:1 hexanes:EtOAc) to give a yellow oil. Flash chromatography (100:1 hexane:EtOAc, then 20:1 hexane:EtOAc) gave 7.73 g (82% yield) of cyclic enol ether **1.145** as a colorless oil whose spectroscopic details were in accordance with that previously reported [77]: R*f* 0.43 (10:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.81-7.78 (m, 4 H), 7.22-7.26 (m, 6 H), 4.42 (dd, *J* = 3.9, 2.9 Hz, 1 H), 4.36-4.33 (m, 1 H), 3.75-3.65 (m, 3 H), 3.150 (s, 3 H), 3.148 (s, 3 H), 2.16-2.06 (m, 3 H), 1.87-1.80 (m, 2 H), 1.73-1.53 (m, 5 H), 1.42-1.35 (m, 3 H), 1.19 (s, 9 H), 0.86 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 153.3, 136.0, 134.4, 129.9, 128.3, 104.5, 93.7, 77.9, 64.2, 52.11, 52.08, 34.3, 32.3, 29.63, 29.60, 29.1 27.8, 27.1, 22.7, 19.5, 13.5.



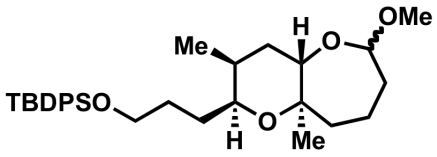
(2*R*,3*S*,5*S*,6*S*)-6-(3-(*tert*-butyldiphenylsilyloxy)propyl)-2-(4,4-dimethoxybutyl)-2,5-dimethyltetrahydro-2*H*-pyran-3-ol 1.148. To **1.146** (675 mg, 1.32 mmol) in CH_2Cl_2 (80.0 ml) at -78^o C was added "acetone free" DMDO (8.25 ml of a 0.2 M solution in

CH_2Cl_2, 1.65 mmol) dropwise. The reaction mixture was warmed to 0 ^oC over 25 min after which it was recooled to -78 ^oC, and $AlMe_3$ (3.30 ml of a 2 M solution in hexane, 6.6 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 8-10 min then warmed to 0 ^oC over 2-3 min at which time it was quenched with sat. pH 7.0 phosphate buffer (aq., 10.0 ml), extracted with CH_2Cl_2 (4 X 30 ml), dried with Na_2SO_4 and concentrated. Flash chromatography (3:1 hexane:EtOAc to 1:1 hexane:EtOAc) gave .351 g (49 % yield) of **1.148** as a colorless oil whose spectroscopic details were in accordance with that previously reported[77]: R_f 0.67 (1:1 hexanes/EtOAc); ^1H NMR (500 MHz, C_6D_6) δ 7.83-7.77 (m, 4 H), 7.27-7.22 (m, 6 H), 4.36 (t, *J* = 4.9 Hz, 1 H), 3.75-3.63 (m, 2 H), 3.50 (m, 1 H), 3.33 (ddd, *J* = 8.3, 4.4, 2.4 Hz, 1 H), 3.16 (s, 6 H), 1.82-1.43 (m, 11 H), 1.40 (ddd, *J* = 12.2, 4.9, 2.4 Hz, 1 H), 1.33-1.25 (m, 1 H), 1.19 (s, 9 H), 1.05 (s, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 136.4, 134.9, 130.3, 128.7, 105.2, 77.2, 71.6, 68.5, 64.7, 52.60, 52.59, 41.50, 37.0, 34.0, 33.7, 30.3, 29.9, 27.5, 19.9, 18.6, 15.4, 13.0.

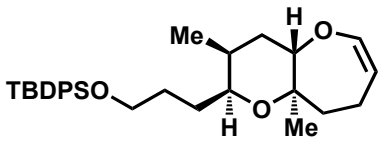


(2*R*,3*S*,5*S*,6*S*)-6-(3-((*tert*-butyl-diphenylsilyl)oxy)propyl)-2-(4-methoxy-pentyl)-2,5-dimethyl-tetrahydro-2*H*-pyran-3-ol 1.147. Alcohol **1.147** was obtained as an undesired product when the procedure to synthesize **1.148** was carried out. R_f 0.70 (1:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = -7.2° (c = 0.9, CH_2Cl_2); ^1H NMR (500 MHz, C_6D_6) δ; 7.80 (dd, *J* = 7.8, 4.4 Hz, 4H), 7.24 (m, 6H), 3.74-6.64 (m, 3H), 3.52 (dd, *J* = 11.7, 4.9 Hz, 1H), 3.35 (dddd, *J* =8.7, 4.3, 2.1, 2.1 Hz, 1H), 3.15 (s, 3H), 1.81-1.26 (m, 15H), 1.14 (s, 9H), 1.08-1.07 (m, 3H), 0.89 (d, *J* =6.8 Hz, 1.5H), 0.89 (d, *J* = 7.3 Hz, 1.5H); ^{13}C NMR (125

MHz, C_6D_6) δ 136.4, 130.3, 128.7, 128.4, 77.3, 77.3, 71.5, 68.6, 68.5, 64.7, 56.1, 56.1, 41.8, 38.0, 37.0, 33.7, 30.3, 30.0, 27.5, 19.7, 19.6, 19.4, 19.3, 15.5, 15.4, 13.0; DEPT (125 MHz, C_6D_6) δ CH_3: 27.5, 19.6, 19.6, 15.5, 15.5, 13.0 CH_2 41.8, 38.0, 37.0, 30.3, 30.0, 19.4, 19.3 CH: 136.4, 130.3, 128.7, 128.4, 77.3, 77.3, 71.5, 68.6, 68.5, 33.7; IR (film) 3400, 2917, 2849, 1540, 1456, 1109 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{32}H_{50}O_4SiNa$ 549.3 ($M+Na^+$), found 549.3; for $C_{32}H_{50}O_4SiK$ 565.3 ($M+K^+$), found 565.3.

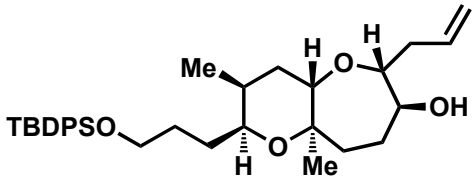


***tert*-butyl-(3-((2*S*,3*S*,4a*S*,9a*R*)-6-methoxy-3,9a-dimethyloctahydro-2*H*-pyrano [3,2*b*]-oxepin-2-yl)propoxy)diphenylsilane 1.149**. To a solution of **1.148** (0.91 g, 1.67 mmol) in benzene (60 ml) at rt was added PPTS (0.75 g, 0.1 mmol). The reaction was heated at reflux for 1 h at which point it was cooled to rt and concentrated. Flash chromatography of the resulting residue (hexanes:EtOAc 20:1) gave 0.77 g (91 % yield) of mixed cyclic acetal (dr = 10:1 α:β) **1.149** as a colorless oil whose spectroscopic details were in accordance with that previously reported[77]: R*f* 0.40 (10:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.83-7.77 (m, 4 H), 7.26-7.22 (m, 6 H), 4.42 (dd, *J* = 8.8, 5.9 Hz, 1 H), 3.99 (dd, *J* = 12.2, 4.9 Hz, 1 H), 3.77-3.65 (m, 2 H), 3.49-3.44 (m, 1 H), 3.26 (s, 3 H), 1.88-1.22 (m, 13 H), 1.20 (s, 3 H), 1.19 (s, 9 H), 0.95 (d, *J* = 6.84 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 136.4, 134.8, 130.3, 128.7, 103.1, 76.7, 71.2, 67.0, 64.7, 55.2, 45.7, 35.7, 35.0, 33.5, 30.2, 29.9, 27.5, 19.8, 19.7, 16.3, 12.9;



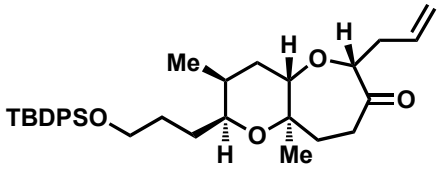
***tert*-butyl(3-((2*S*,3*S*,4a*S*,9a*R*)-3,9a-dimethyl-3,4,4a,8,9,9a-hexahydro-2*H*-pyrano[3,2-**

***b*]oxepin-2-yl)propoxy)diphenylsilane 1.150**. To **1.149** (1.04 g, 2.04 mmol) in CH_2Cl_2 (10.0 ml) at -78° C was added DIPEA (3.56 mL, 20.48 mmol) followed by TMSOTf (1.74 ml of a 1 M solution in Et_2O, 3.48 mmol). The reaction mixture was warmed to 0 °C over 1 h at which point the reaction mixture was concentrated. Flash chromatography using neutralized silica (hexanes:EtOAc 50:1) gave 0.887 g (90 % yield) of **1.150** as a colorless oil whose spectroscopic details were in accordance with that previously reported [77]: R_f 0.71 (10:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.82-7.77 (m, 4 H), 7.25-7.22 (m, 6 H), 6.35 (dd, *J* = 7.3, 2.4 Hz, 1 H), 4.53 (ddd, *J* = 7.3, 7.3, 2.9 Hz, 1 H), 3.75-3.64 (m, 2 H), 3.61 (dd, *J* = 11.7, 4.9 Hz, 1 H), 3.4 (ddd, *J* = 8.3, 4.4, 2.5 Hz, 1 H), 1.99-1.71 (m, 5 H), 1.63-1.25 (m, 6 H), 1.19 (s, 9 H), 1.09 (s, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 147.5, 136.4, 134.9, 130.3, 128.7, 108.2, 80.7, 78.1, 71.3, 64.7, 42.1, 35.4, 33.3, 30.2, 29.7, 27.5, 22.0, 19.9, 13.7, 12.8.

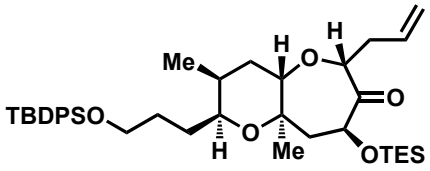


(2*S*,3*S*,4a*S*,6*R*,7*S*,9a*R*)-6-allyl-2-(3-(*t*-butyl-diphenyl-silyloxy)-propyl)-3,9a-di-methyl octahydro-2*H*-pyrano[3,2-*b*]oxepin-7-ol 1.153. To the enol ether **1.151** (0.210 g, 0.439 mmol) in CH_2Cl_2 (60 ml) at -78 °C was added "acetone free" DMDO (2.41 ml of a 0.2 M soln. in CH_2Cl_2, 0.483 mmol) dropwise. The reaction mixture was warmed to 0 °C while stirring over 30 min at which point allyl magnesium chloride (4.40 ml of a 2 M soln. in THF, 8.78 mmol) was added at once. The mixture was warmed to rt over 30 min, quenched with sat. NH_4Cl (aq., 20 ml), extracted with CH_2Cl_2 (3 X 50 ml), dried (Na_2SO_4), and then concentrated. Flash chromatography (hexane:EtOAc 5:1 to 3:1) gave 0.146 g (62 % yield) of **1.153** as a colorless oil whose spectroscopic details were in

accordance with that previously reported [77]: R_f 0.55 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.83-7.8 (m, 4 H), 7.26-7.22 (m, 6 H), 5.95-5.85 (m, 1 H), 5.06-4.99 (m, 2 H), 3.80-3.66 (m, 3 H), 3.55 (ddd, *J* = 6.4, 6.4, 2.4 Hz, 1 H), 3.51-3.45 (m, 2 H), 2.23-2.06 (m, 3 H), 1.84-1.28 (m, 10 H), 1.20 (s, 3 H), 1.19 (s, 9 H), 0.95 (d, *J* = 7.3 Hz, 1 H); ^{13}C NMR (125 MHz, C_6D_6) δ 136.4, 136.1, 134.9, 130.2, 117.8, 85.2, 77.1, 75.4, 74.1, 71.4, 64.8, 40.1, 36.2, 35.4, 33.5, 30.6, 30.3, 29.9, 27.5, 19.9, 16.3, 13.1.



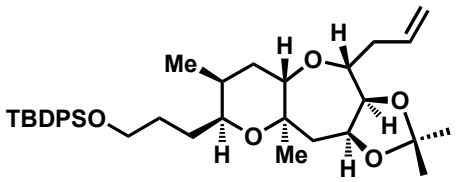
(2*S*,3*S*,4a*S*,6*R*,9a*R*)-6-allyl-2-(3-(*tert*-butyl-diphenylsilyl-oxy)propyl)-3,9a-dimethyl hexahydro-2*H*-pyrano[3,2-*b*]oxepin-7(3*H*)-one 1.154. To the alcohol **1.153** (0.252 g, 0.47 mmol) in CH_2Cl_2 (20 ml) at rt was added 4Å MS (0.300 g), NMO (0.275 g, 2.35 mmol) and TPAP (ca 10 mg). The reaction was stirred at this temperature for 3 h at which point the reaction was loaded directly onto silica gel. Flash chromatography (hexane:EtOAc 20:1 to 10:1) gave 0.233 g (93 % yield) of ketone **1.154** as a colorless oil whose spectroscopic details were in accordance with that previously reported: R_f 0.35 (3:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.82-7.76 (m, 4 H), 7.26-7.22 (m, 6 H), 5.85 (dddd, *J* = 17.1, 10.3, 7.3, 7.3 Hz, 1 H), 5.03 (m, 0.5 H), 5.01 (m, 0.5 H), 4.99 (m, 1 H), 3.78 (dd, *J* = 6.8, 5.4 Hz, 1 H), 3.73-3.62 (m, 2 H), 3.39 (ddd, *J* = 7.3, 4.4, 2.4 Hz, 1 H), 3.07 (dd, *J* = 12.2., 4.9 Hz, 1 H), 2.52 (ddd, *J* = 12.7, 12.7, 5.4 Hz, 1 H), 2.37-2.25 (m, 2 H), 2.20-2.14 (m, 1 H), 1.75-1.40 (m, 8 H), 1.29-1.21(m, 1 H), 1.19 (s, 9 H), 1.13 (s, 3 H), 0.76 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 214.8, 136.4, 134.8, 134.0, 130.3, 128.4, 118.1, 87.3, 79.8, 76.5, 71.5, 64.6, 39.8, 38.1, 37.9, 35.0, 33.5, 30.1, 29.7, 27.5, 19.8, 15.0, 12.8.



(2S,3S,4aS,6R,8S,9aR)-6-allyl-2-(3-((*t*-butyldiphenylsilyl)oxy)propyl)-3,9a-dimethyl-8-((triethylsilyl)oxy)hexahydro-2H-pyrano[3,2-b]oxepin-7(3H)-one 1.155. To a solution of ketone **1.154** (240 mg, 0.450 mmol) in THF (12 mL) at rt was added TESCl (0.375 mL, 2.25 mmol) and Et_3N (0.312 mL, 2.25 mmol). The reaction mixture was cooled to −78 °C and treated with LiHMDS (1.0 M in THF, 1.34 mL, 1.34 mmol). After being stirred at −78 °C for 50 min the reaction was warmed to rt and diluted with hexanes (10 mL). The diluted reaction mixture was loaded onto a plug of neutral silica gel eluting with 10:1 hexanes:EtOAC and then concentrated to afford crude enol silyl ether, which was used in the oxidation reaction without further purification.

To a solution of the above silyl enol ether in CH_2Cl_2 (5.0 mL) at rt was added $NaHCO_3$ (0.188 g, 2.24 mmol) and *m*CPBA (0.077 g, 0.449 mmol). After 45 min, the reaction was quenched saturated aqueous NaS_2O_3 solution (5 ml). The aqueous phase was extracted with CH_2Cl_2 (3 x 20). The extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (hexane:EtOAc 20:1 to 10:1) gave 0.231 g (77 % yield) of **1.155** as a colorless oil. R*f* 0.2 (10:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = +1.6° (c = 1.1, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.84-7.76 (m, 4 H), 7.28-7.22 (m, 6 H), 5.89 (dddd, *J* = 17.2, 10.3, 7.0, 7.0 Hz, 1 H), 5.09-5.01 (m, 2 H), 4.79 (dd, *J* = 12.1, 3.8 Hz, 1 H), 3.85 (dd, *J* = 7.0, 5.4 Hz, 1 H), 3.76-3.63 (m, 2 H), 3.42-3.37 (m, 1 H), 3.05 (dd, *J* = 12.1, 4.6 Hz, 1 H), 2.45-2.37 (m, 1 H), 2.18 (dd, *J* = 13.4, 3.9 Hz, 1 H), 2.10 (t, *J* = 12.3 Hz, 1 H), 1.80-1.40 (m, 9 H), 1.29 (s, 3 H), 1.19 (s, 9 H), 1.06 (dd, J = 8.1, 7.7 Hz, 9 H), 0.74-0.66 (m, 9 H). ^{13}C NMR (125 MHz, C_6D_6) δ 136.4, 133.7, 130.3, 128.7, 128.7,

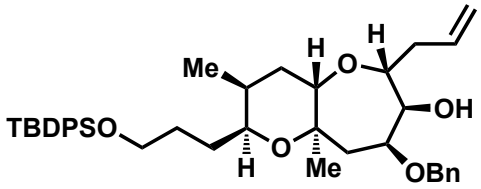
118.4, 86.7, 79.7, 74.1, 71.1, 64.6, 50.8, 38.7, 34.5, 33.4, 30.6, 30.1, 29.6, 27.5, 19.8, 15.8, 12.9, 7.5, 5.9. IR (film) 3400, 2933, 2849, 1731, 1462, 1428, 1110 cm^{-1}; HRMS (*m/z*) calcd for $C_{39}H_{60}O_5Si_2Na$ 687.3877 (M^+Na^+), found 687.3869.



(3-((3aS,4aR,6S,7S,8aS,10R,10aR)-10-allyl-2,2,4a,7-tetramethyloctahydro-3aH-[1,3]-dioxolo[4,5-e]pyrano[3,2-b]oxepin-6-yl)propoxy)(tert-butyl)diphenylsilane 1.161. To a solution of **1.155** (.231 g, .363 mmol) in CH_2Cl_2 (5 mL) and MeOH (5 mL) at 0 °C was added CSA (ca .01 g). The reaction was stirred for 30 min at which point it was concentrated. The resulting residue was passed through a silica plug to give the crude hydroxy ketone **1.157** which was taken on into the reduction step without further purification.

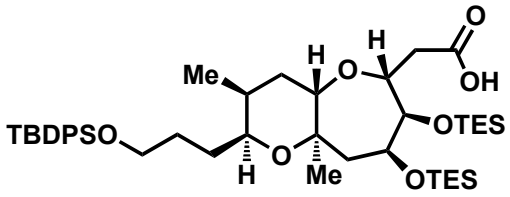
To a solution of crude hydroxy ketone **1.157** (0.190 g, .345 mmol) from above in CH_2Cl_2 (6.5 mL) at -78 °C was slowly added *i*Bu_2AlH (0.605 ml of 1.5 M solution in toluene, .91 mmol). After stirring at this temperature for 45 min, a second portion of *i*Bu_2AlH (0.387 ml of 1.5 M solution in toluene, 0.58 mmol) was added. The reaction was allowed to stir for an additional 45 min at -78 °C. The reaction was quenched by the addition of saturated aqueous potassium sodium tartrate (10 mL). The resultant mixture was diluted with EtOAc and stirred at rt until the layers became clear. The aqueous phase was extracted with EtOAc (3 x 100 mL), dried (Na_2SO_4), and concentrated. Flash Chromatography (hexane:EtOAc 10:1) gave 0.175 g (92 % yield) of **1.159** as a colorless oil as a 10:1 mixture of diasterisomers favoring **1.159**. **1.159** was characterized as the

acetonide: R_f 0.30 (1:1 hexanes/EtOAc); $[\alpha]_D^{20}$ = +8.3° (c = 0.07, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 7.81-7.79 (m, 4 H), 7.25-7.23 (m, 6 H), 6.08 (dddd, *J* = 12.1, 10.3, 6.7, 6.8 Hz, 1 H), 5.22-5.18 (m, 1H), 5.14-5.11 (m, 1H), 4.39 (ddd, *J* = 10.7, 6.6, 6.6 Hz, 1H), 3.93 (dd, *J* = 9.7, 7.3 Hz, 1H), 3.71 (ddd, *J* = 10.0, 6.6, 6.6 Hz, 1H), 3.66 (ddd, *J* = 10.0, 6.6, 6.6 Hz, 1H), 3.40 (m, 2H), 3.33 (dd, *J* = 12.2, 4.9 Hz, 1H), 2.74-2.70 (m, 1H), 2.38 (dd, *J* = 13.2, 6.3 Hz, 1H), 2.35-2.30 (m, 1H), 2.06 (dd, *J* = 13.2, 10.7, 1H), 1.73-1.44 (m, 5H), 1.43 (s, 3H), 1.23 (s, 3H), 1.95 (s, 9H), 0.95 (s, 3H), 0.76 (d, *J* = 6.84 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 136.4, 136.4 136.0, 134.8, 134.8, 130.3, 128.7, 117.1, 108.4, 83.5, 81.7, 80.6, 74.9, 74.7, 70.9, 64.6, 45.3, 38.6, 34.6, 33.4, 30.2, 29.6, 28.0, 27.5, 24.6, 19.8, 14.6, 13.2; IR (film) 2934, 2893, 1461, 1428, 1380, 1103 cm^{-1}; ESI/MS (*m/z*) calcd for $C_{39}H_{62}O_5Si_2Na$ 689.7 ($M+Na^+$), found 689.7; for $C_{36}H_{52}O_5SiNa$ 615.3482 ($M+Na^+$), found 615.3480.



(2S,3S,4aS,6R,7S,8S,9aR)-6-allyl-8-(benzyloxy)-2-(3-((*tert*-butyl-diphenylsilyl)oxy)-propyl)-3,9a-dimethyloctahydro-2H-pyrano[3,2-b]oxepin-7-ol. 1.114 To a solution of diol **1.159** (0.015 g, 0.027 mmol) in MeOH (2.5 mL) was added Bu_2SnO (.0074 g.030 mmol). The reaction mixture was heated at reflux for 2.5 h and then cooled to rt. The solvent was evaporated and to the resulting residue was added DMF (1.25 mL) followed by CsF (0.007 mg, .041 mmol), then BnBr (0.030 mL, 0.041 mmol). The reaction was allowed to stir for 12 h. The reaction was loaded directly onto a column. Flash chromatography (hexanes:EtOAc 10:1 to 5:1 to 3:1) gave 0.13 mg (77 % yield) of the

monobenzyl coupling precursor **1.114** as a colorless oil. R_f 0.60 (3:1 hexanes:ethyl acetate). $[\alpha]_D^{20}$ = +1.9° (c = 0.16, THF); 1H NMR (500 MHz, C_6D_6) 7.84-7.78 (m, 4H), 7.30-7.14 (m, 10H), 7.10 (t, *J* = 7.3 Hz, 1H), 5.86 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1H), 5.03 (d, *J* = 15.1 Hz, 1H), 5.00 (d, *J* = 9.3 Hz, 1H), 4.40 (d, *J* = 12.2 Hz, 1H), 4.26 (d, *J* = 11.7 Hz, 1H), 3.98-3.93 (m, 2H), 3.86 (ddd, *J* = 6.4, 6.4, 1.5 Hz, 1H), 3.75 (ddd, *J* = 10.3, 6.4, 6.4 Hz, 1H), 3.70 (ddd, *J* = 9.8, 6.8, 6.8 Hz, 1H), 3.61 (d, *J* = 10.7 Hz, 1H), 3.45 (ddd, *J* = 7.8, 4.4, 3.4 Hz, 1H), 2.56 (dd, *J* = 12.2, 12.2 Hz, 1H), 2.25-2.18 (m, 2H), 1.92 (dd, *J* = 13.2, 2.0 Hz, 1H), 1.80 (m, 1H), 1.70-1.45 (m, 4H), 1.37-1.20 (m, 2H), 1.19 (m, 9H), 1.16 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6); 135.9, 135.0, 134.4, 129.8, 128.5, 128.1, 127.9, 127.7, 117.0, 81.9, 76.9, 76.2, 74.5, 74.2, 70.7, 70.7, 64.3, 41.3, 39.9, 34.5, 32.9, 29.8, 29.3, 27.0, 19.3, 16.3, 12.5; IR (neat) 3454, 2932, 2860, 1468, 1428, 1383, 1108 cm^{-1}; ESI/MS (m/z) calcd for $C_{40}H_{54}O_5SiNa$ 665.4 (M^+Na^+), found 665.3.



2-((2S,3S,4aS,6R,7R,8S,9aR)-2-(3-((*t*-butyldiphenylsilyl)oxy)propyl)-3,9a-dimethyl-7,8-bis((triethylsilyl)oxy)octahydro-2H-pyrano[3,2-b]oxepin-6-yl)acid 1.177. To a solution of diol **1.159** (0.150 g, 0.287 mmol) in CH_2Cl_2 (15 mL) at 0 °C were added Et_3N (1.0 mL, 4.30 mmol) and TESOTf (0.325 mL, 2.87 mmol). The reaction mixture was stirred at 0 °C for 1 h at which point the reaction was treated with saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (4 x 20 mL). The extracts were combined, dried (Na_2SO4), and concentrated. The resulting residue was passed

through a plug of silica gel to give crude product, which used was in oxidation reaction without further purification.

To a solution of crude bis-TES (0.224 g, 0.287 mmol) from above in THF/*t*-BuOH/H_2O (5:5:1, v/v, 10 mL) at rt was added NMO (0.104 g, 0.896 mmol) and OsO_4 (0.360 mL of a 0.1 M soln. in THF, 0.036 mmol). The reaction mixture was stirred at room temperature for 6 h at which point saturated aqueous $NaHCO_3$ (10 mL) was added. The aqueous phase was extracted with EtOAc (4 x 20 mL). The extracts were combined, dried (Na_2SO_4), and concentrated. The residue was passed through a plug of silica gel to give crude diol, which used was in the next reaction without further purification.

To a solution of crude diol (0.208 g, 0.255 mmol) in benzene (15 mL) at rt was added $Pb(OAc)_4$ (0.142 mg, 0.320 mmol). The reaction mixture was stirred at room temperature for 30 min and then concentrated. The resulting residue was passed through a pad of silica gel to give crude aldehyde, which used was in the next reaction without further purification.

To the crude aldehyde (0.195 g, 0.249 mmol) from above in *t*BuOH THF/*t*-BuOH/H_2O (1:1:1, v/v, 17 mL) at rt were added 2-methyl-2-butene (1.20 mL, 4.20 mmol) followed by $NaClO_2$ (0.095 g, 1.05 mmol) and $NaH_2PO_4.H_2O$ (0.125 g, 1.05 mmol). After stirring rapidly for 3 h the reaction mixture was diluted with sat. NH_4Cl (aq., 10 ml). The aqueous phase was extracted with CH_2Cl_2 (6 X 25 ml). The extracts were combined, dried (Na_2SO_4) and concentrated. Flash chromatography (hexane:EtOAc 10:1 to 3:1) gave 0.192 g (84% yield from **1.159**) of **1.177** as a colorless oil. R_f 0.30 (3:1 hexanes:ethyl acetate). $[\alpha]_D^{20}$ = -7.0° (c = 0.19, THF); ^{1}H NMR (500 MHz, C_6D_6); 7.79-7.75 (m, 4H), 7.26-7.21 (m, 6H), 4.31 (dd, *J* = 7.1, 7.1 Hz, 1H), 4.23 (dd, *J* = 10.7, 6.8

Hz, 1H), 4.03-3.99 (m, 2H), 3.68 (ddd, *J* = 10.3, 6.4, 6.4 Hz, 1H), 3.63 (ddd, *J* = 10.3, 6.4, 6.4 Hz, 1H), 3.45-3.41 (m, 1H), 2.75 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.59 (dd, *J* = 15.1, 7.8 Hz, 1H), 2.40 (dd, *J* = 15.1, 6.8 Hz, 1H), 1.80-1.69 (m, 2H), 1.68-1.62 (m, 1H), 1.60-1.45 (m, 3H), 1.34-1.27 (m, 2H), 1.26 (s, 3H), 1.16 (s, 9H), 1.09 (t, *J* = 7.8 Hz, 9H), 1.03 (d, *J* = 8.3 Hz, 3H), 0.97 (t, *J* = 7.8 Hz, 9H), 0.72 (qd, *J* = 7.8, 2.0 Hz, 6H), 0.60 (qd, *J* = 7.8, 2.0 Hz, 6H); ^{13}C NMR (125 MHz, C_6D_6); 176.2, 135.8, 134.3, 134.2, 129.6, 128.1, 81.3, 80.0, 73.9, 72.4, 70.6, 68.9, 64.1, 45.2, 39.7, 34.3, 32.9, 30.0, 29.6, 29.2, 26.9, 19.3, 16.5, 12.2, 7.0, 6.9, 5.1, 4.9; IR (neat) 2955, 2878, 1713, 1464, 1426, 1382, 1107 cm^{-1}; ESI/MS (m/z) calcd for $C_{44}H_{74}O_7Si_3Na$ 821.5 (M^+Na^+), found 821.4.

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CHAPTER 2

OLEFINIC-LACTONE CYCLIZATIONS: TOTAL SYNTHESIS OF (-)-MUSCONE AND (+)-MUSCOPYRIDINE

Introduction

Macrocyclic products are abundant in nature and the diversity in which nature has created marcocyclic systems has prompted synthetic chemists to develop equally diverse strategies in which to construct them. Common synthetic routes to such compounds often involve a macrocyclization step, which can prove challenging. Synthetic targets containing a lactone or lactam can readily be accessed through a macrolactonization or macrolactamization reaction.[1] However, when synthesizing targets lacking these functionalities, synthetic chemists have been forced to turn to other, sometimes less obvious, disconnections to generate the macrocycle.[2,3] In this chapter, studies illustrating the synthetic advances in the generation of all-carbon macrocycles will be discussed.

Ring-closing metathesis has become a popular approach for the generation of all-carbon macrocycles. Ring closing alkene metathesis (RCM) or ring closing alkyne metathesis (RCAM) are common methods to construct large rings including those of both natural and non-natural origins.[4-8] Demonstration of RCM and RCAM in the total synthesis of the natural product civetone **2.1** is shown in Figure 2.1.[9]

Grubbs' first and second generation catalysts (Figure 2.2) used for RCM are

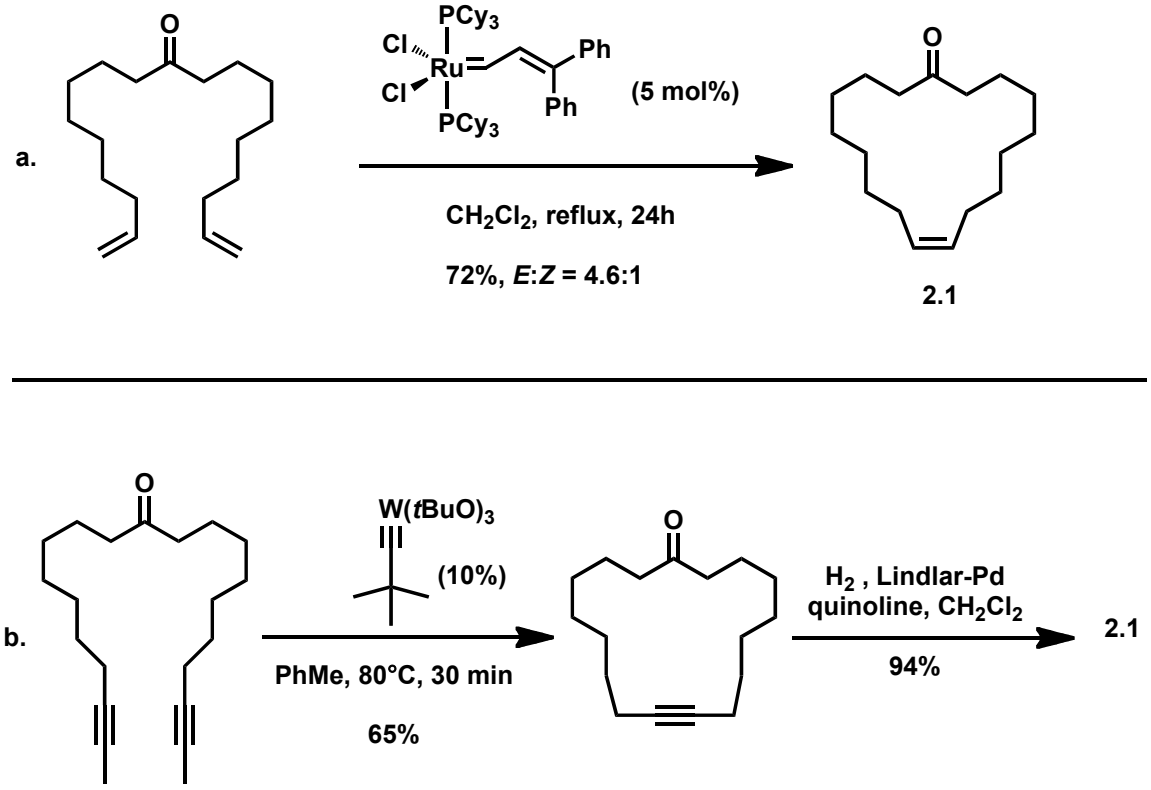


Figure 2.1. Synthesis of civetone via (a) RCM and (b) RCAM

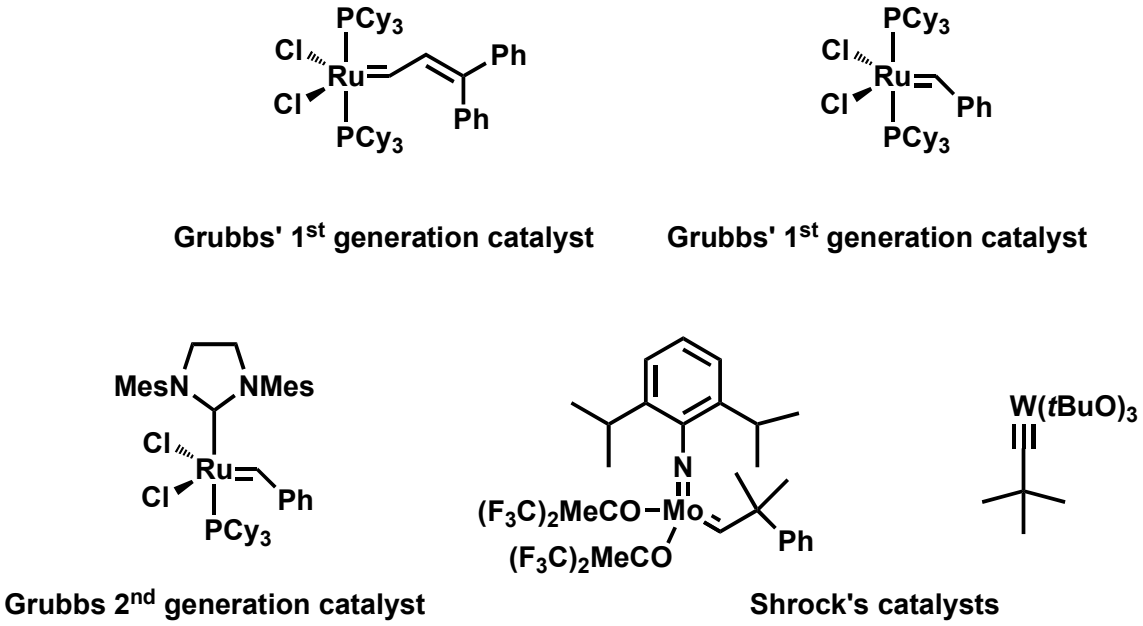


Figure 2.2. Ring closing metathesis catalysts

commercially available, easy to handle and stable at room temperature. The ruthenium based Grubb's catalysts display high functional group tolerance, selectivity, and have proven useful under mild reaction conditions.[5]

The Shrock molybdenum (VI) and tungsten (VI) based catalysts are known as Schrock alkylidenes. The Schrock catalyst system, tris-(*tert*-butoxy)-(2,2-dimethyl-propylidyne)tungsten(VI) is also able to affect RCAM and related polymerizations.[6,8,10]

Numerous studies on RCM have defined the scope of this method and have provided insights into the essential parameters required for successful macro ringclosing diene metathesis. Many successful synthetic endeavors have suggested the necessity of a properly positioned relay moiety (ester, ketone amide, etc.) to promote large ring cyclization. In Fürstner's synthesis of lasiodiplodin, the success of the macrocyclization reaction is attributed to the coordination of the ester onto the ruthenium catalyst as shown in Figure 2.3.[13] This coordination lowers the entropic energy barrier and/or the build up of ring strain associated with assembling the diene residues of **2.2**. The distance between the diene residues and the ester are important parameters for the successful RCM of a macrocyclic ring.[11,13]

Relay moieties can often lead to difficulties in both the synthesis of the molecule as well as in the RCM reaction. More often than not, the relay moiety is imbedded within the macrocycle and unless the relay moiety can be removed following cyclization, the synthetic disconnection of all-carbon macrocycles may prove to be a difficult task. Chelation with the relay moiety can lead to a stable intermediate that can result in catalyst sequestering as shown in the synthesis of zeronal (Figure 2.4).[13] When Fürstner and coworkers attempted RCM of diene **2.3** bearing the dithiane, only starting material was

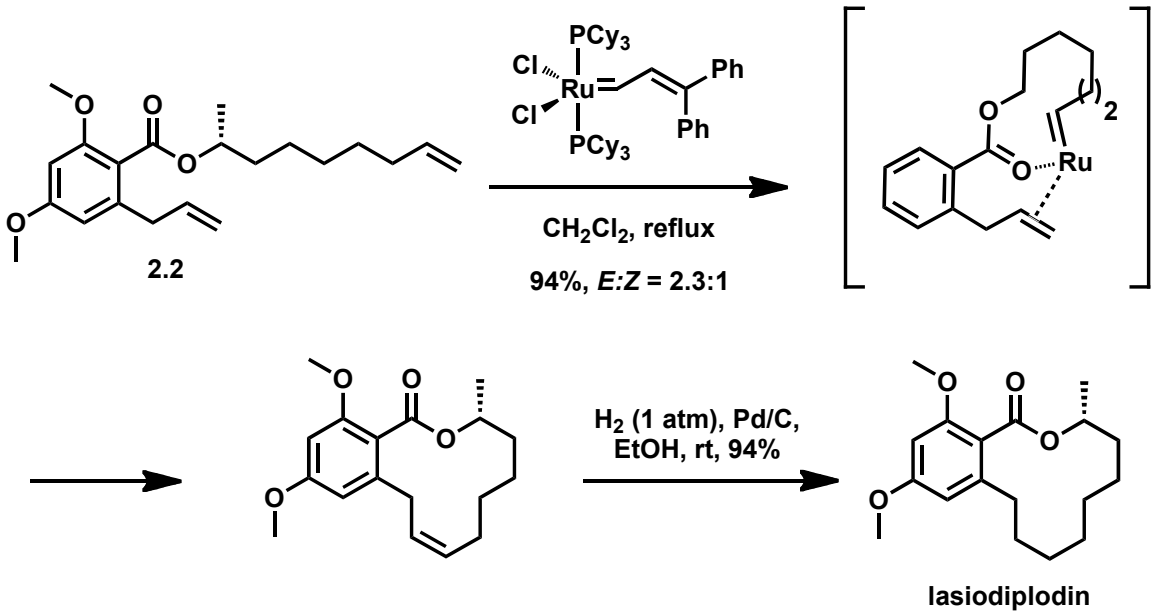


Figure 2.3. Fürstner's synthesis of lasiodiplodin

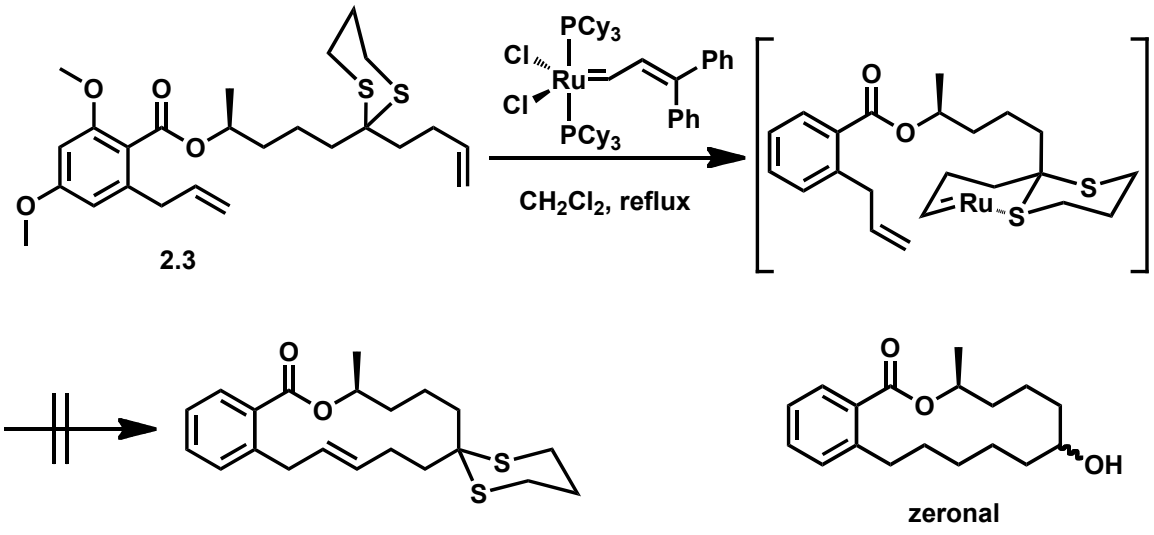


Figure 2.4. Fürstner's attempted RCM of diene **2.3** towards the synthesis of zerona

obtained. This report, as with others, have indicated an incompatibility of Grubbs' catalysts with substrates containing sulfur as well as various other donor sites.[15,16] Due to these set backs, other methods have arisen to accommodate retrosyntheses lacking RCM to generate a macrocycle. Many examples exist; however, recent reports in the failure of RCM and the success of other methods to construct the macrocycle in kendomycin is representitive (Figure 2.5).[17]

The diverse biological profile and challenging structure of kendomycin has inspired a number of groups to initiate a program towards its synthesis. To date, three total syntheses and one formal synthesis have been reported.[18-22] The underlying problem for these approaches has been the formation of the strained macrocyclic ring through RCM and alternative disconnections have been required. For example, macrocyclizations were performed using *C*-glycosidation,[18] Barbier-type addition,[21] Prins reaction,[22] and, perhaps most strikingly, all attempts to achieve macrocyclization at C13-C14 by ring-closing metathesis (RCM) have been unsuccessful due to low yields and formation of the undesired C13,C14-*Z*-olefin. Although the undesired *Z* olefin has, in some cases, been isomerized to the correct *E* olefin the transformation has required multiple steps after the initial RCM.[20]

A creative disconnection of kendomycin was proposed by Mulzer et al. after they tested a variety of alternate locations for RCM disconnections that proved to be unsuccessful.[17] They proposed a photo-Fries disconnection that required macrolactone **2.4** as a key intermediate to construct the all carbon *ansa*-macrolide **2.5.** The macrolactone was assembled from *seco*-acid **2.6** using Keck-Boden conditions.[23] The macrolactone

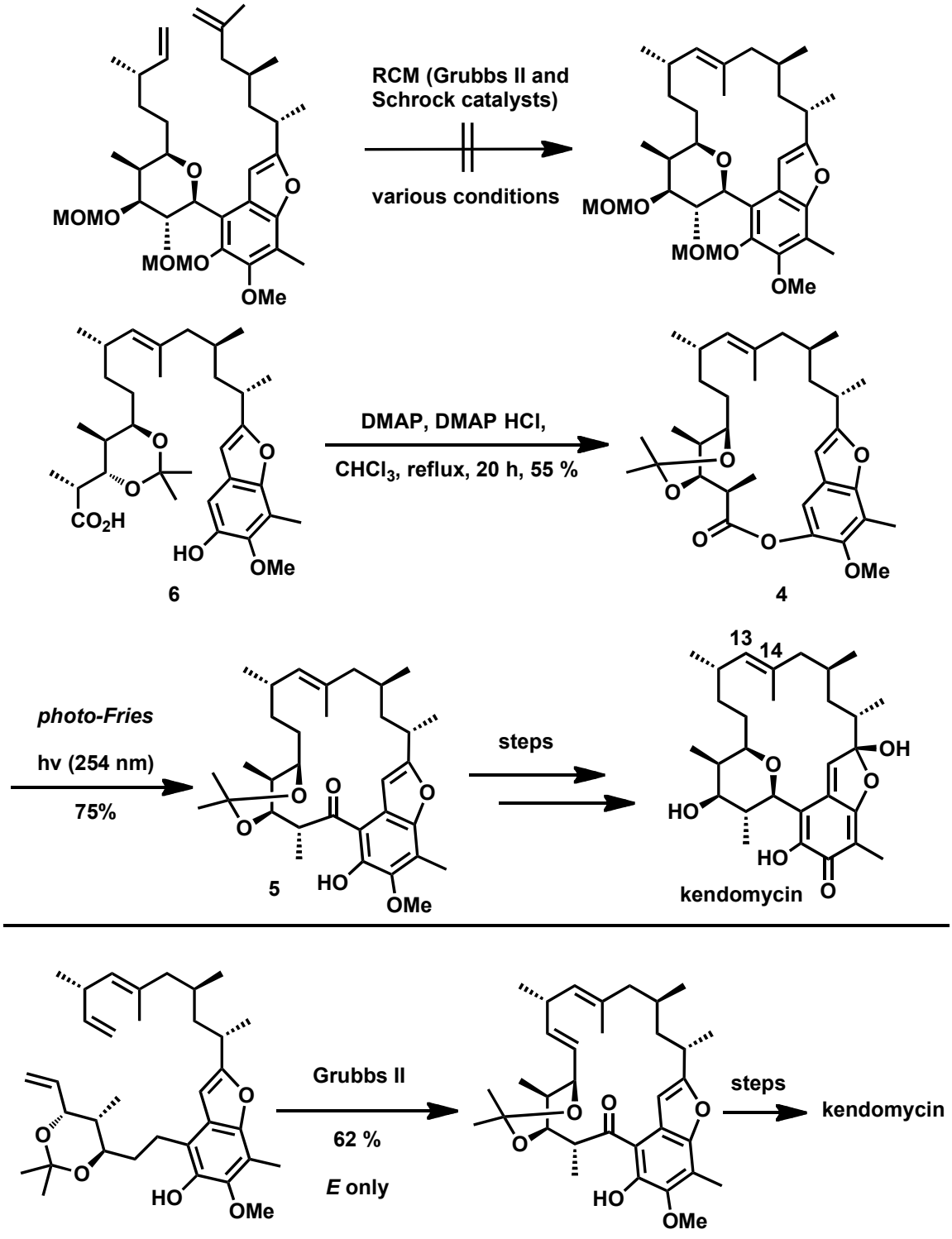


Figure 2.5. Failure of RCM at C13 and C14 and success of a photo-Fries reaction to form the macrocyclic skeleton of kendomycin

underwent clean photo-Fries rearrangement to give the ketone **2.5** that was carried on to give kendomycin. In contrast to Furstner's unsuccessful results, Mulzer was able to utilize a RCM strategy towards kendomycin (Figure 2.5), which again reemphasizes the ability of RCM for connecting diene residues.[17]

Other natural products that have required methods alternative to RCM to achieve their synthesis include, bryostatin,[24] epothilone,[25,26] manzamine[27] and countless others. All of these natural products required other means to construct their macrolide due to low yields or complete failure of RCM.

Aware of the difficulties associated with the synthesis of all-carbon macrocycles, we decided to investigate their formation using our previously disclosed reduced titanium ethylidene conditions that effect olefinic-ester metathesis.[28] Central to the idea is the formation of a cyclic enol ether imbedded in a macrocycle through an olefinic-lactone cyclization, followed by its ring expansion to an all-carbon macrocycle.[29]

Prior to our development of this methodology, our group employed a two-step sequence towards the generation of cyclic enol ethers (Figure 2.6).[30,31] The acyclic enol ether was accessed via olefination of an ester using stoichiometric amounts of a titanium alkylidene reagent (ie. Tebbe's reagent,[32,33] Petasis reagent,[34] and the Takai-Utimoto reagent[35-37]) and was subseuently subjected to RCM conditions using Grubbs' or Schrock's catalyst to give a cyclic enol ether. Rainier et al. were the first to describe the use of Grubbs' second generation catalyst to affect RCM of olefinic enol ethers.[31] The two-step synthesis of enol ethers was proven to be an effective method to synthesize polycyclic ether natural products in the Rainier lab.[38-41] A more efficient method to

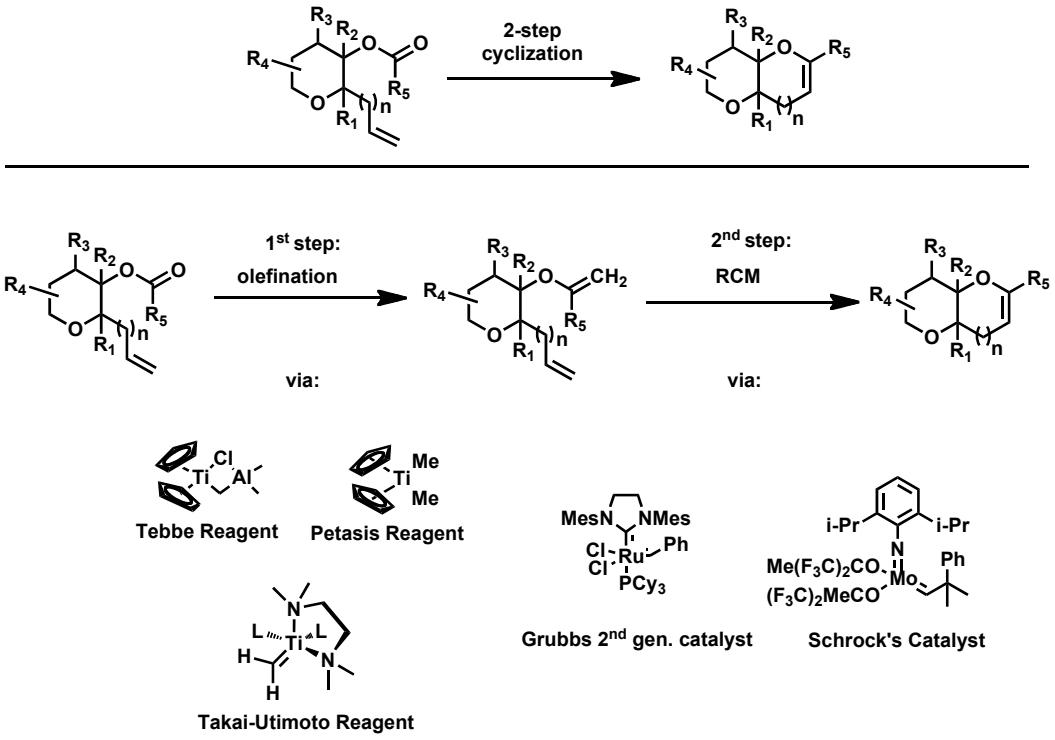


Figure 2.6. General scheme for the two-step conversion of esters to cyclic enol ethers

synthesize enol ethers would bypass the acyclic enol ether intermediate and some successes have been reported.

Nicolaou and coworkers reported olefinic-ester cyclization reactions using the Tebbe and Petasis reagents to generate fused ether compounds (Figure 2.7).[42,43] At the time, they proposed that cyclic enol ethers resulted from titanium alkylidene-mediated RCM of acyclic enol ether intermediates. Despite Nicolaou's impressive one-step sequence, this method has been reported by a number of groups to give variable results.[30,34]

More recently, Takeda and coworkers described the one-step generation of cyclic enol ethers from the corresponding thioacetal-esters using stoichiometric amounts of the titanium catalyst $Cp_2Ti[P(OEt)_3]_2$ (Table 2.8).[45] Their method delivers five-, six-, and seven-membered cyclic enol ethers in good yields from alkyl bis(phenylthio)alkanoates without oligomer formation. Impressively, ester **2.7** was transformed into the nine-membered cyclic enol ether **2.8** with high stereoselectivity.

Rainier and coworkers found that the *in situ* generated titanium-methylidene reagent could affect a one step olefinic-ester cyclization during model studes directed towards the synthesis of hemibrevetoxin B and gambierol.[31,39,40] When compound **2.9** was treated with the titanium-methylidene reagent, a mixture of cyclic **2.10** and acyclic enol ether **2.11** in a 5:3 ratio was isolated (Figure 2.9). To disprove the possibility of a titanium alkylidene-mediated RCM of a transiently formed acyclic enol ether, **2.11** was isolated and resubjected to the titanium-methylidene reagent. This experiment failed to produce cyclic enol ether and led to the hypothesis that **2.10** was formed from a olefin/carbonyl metathesis pathway.

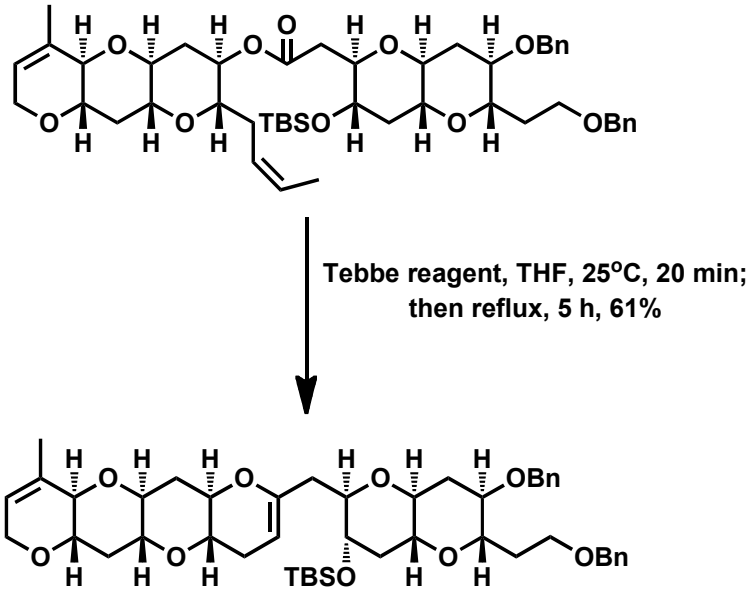


Figure 2.7. Nicolaou's synthesis of the hexacyclic polyether using Tebbe's reagent

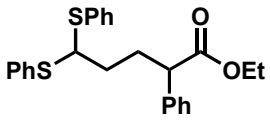
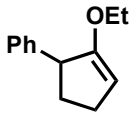
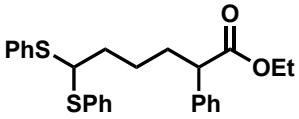
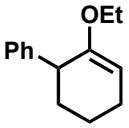
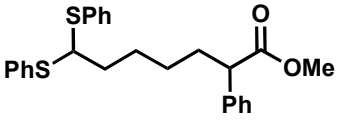
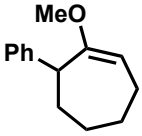
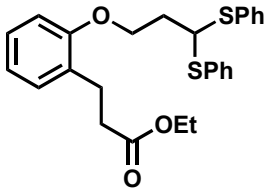
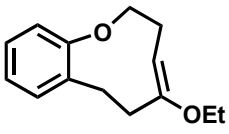
ester-dithiane	$Cp_2Ti[P(OEt)_3]_2$, THF, reflux	cyclic enol ether	yield
			62%
			53%
			68%
 2.7		 2.8	62%

Table 2.8. Takeda's one-step synthesis of enol ethers

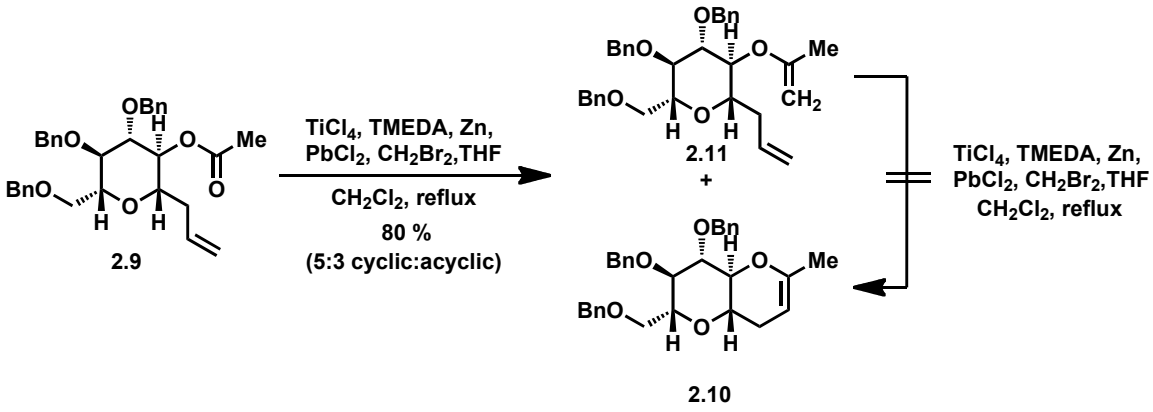
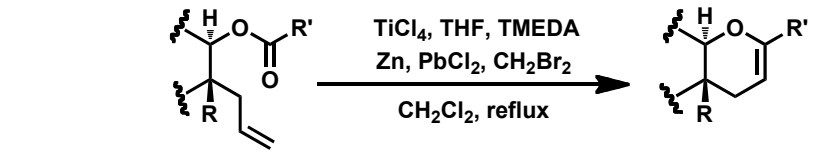


Figure 2.9. Olefinic-ester cyclization to give a mixture of cyclic and acyclic enol ether

Interestingly, Rainier and Majumder found that the enol ether could be obtained directly when modifying the substrate to contain a sterically hindered ester (Table 2.10).[46] By incorporating a hindered ester, the titanium methylidene reagent would preferentially react with the olefin first followed by cyclization onto the carbonyl of the ester. As seen in the case of substrates **2.12** and **2.13** , the esters were significantly hindered compared to the olefins. When these substrates were subjected to the titanium methylidene reagent cyclic enol ether was isolated in >95:5 ratio. When a hindered olefin was employed, as with substrate **2.14**, the titanium methylidene reagent was reactive towards the carbonyl first to give a mixture of acyclic enol ether and cyclic enol ether in a 1.3:1 ratio. The fact that we could bypass the acyclic enol ether intermediate by using a hindered ester was a significant step into understanding the mechanism of this transformation.

Another significant discovery was made during Rainier and Dr. Scott Roberts' work towards gamberic acid A.[41] They found that a difference in the product distribution (acyclic vs. cyclic enol ether) could be controlled by utilizing a more substituted titanium alkylidene reagent (Figure 2.11). Upon the construction of the B ring of gamberic acid A using the titanium methylidene reagent, only the acyclic enol ether resulted. However, when the titanium ethylidene reagent was employed, the reaction led to the exclusive formation of cyclic enol ether **2.15**. Much like the directed reactivity when using hindered esters to promote carbonyl-olefin metathesis, it was believed that the reactivity of the more substituted alkylidene was also due to steric interactions.

It has been previously proposed that mixed metalloid species **2.16** and the titanium alkylidene species **2.17** are in equilibrium. Based on the hypothesis



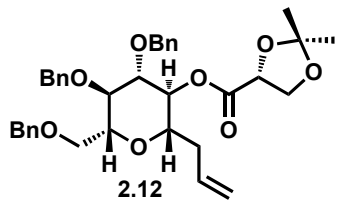
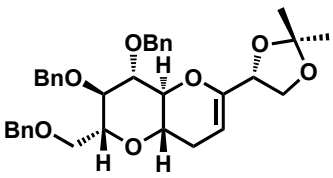
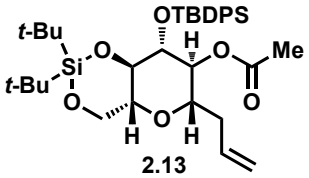
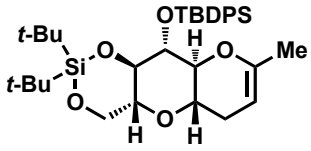
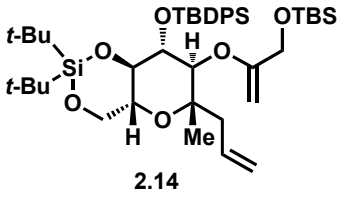
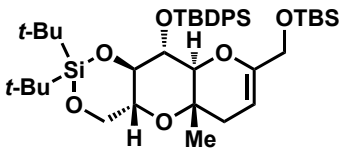
starting material/ acyclic enol ether	cyclic enol ether	yield (cyclic:acyclic)
 2.12		71 % (>95:5)
 2.13		84 % (>95:5)
 2.14		77 % (1.3:1)

Table 2.10. One step conversion of bulky ester-olefin systems to cyclic enol ethers

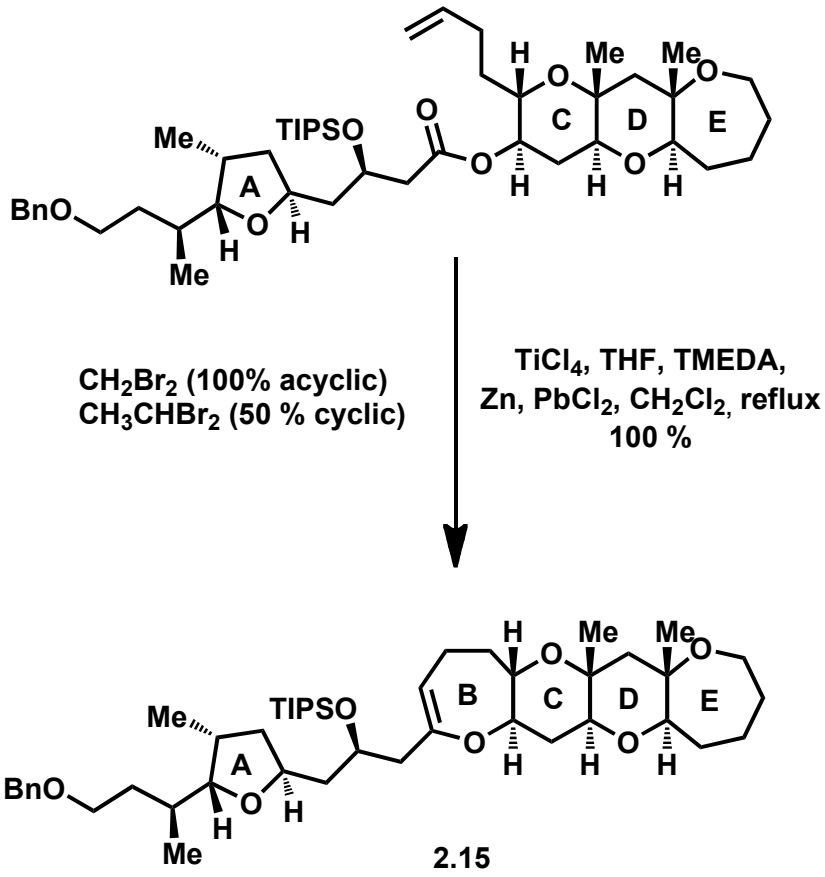


Figure 2.11. Rainier and Roberts' synthesis of the A-E ring fragment of gambieric acid A

that the mixed metalloid species is reactive towards carbonyls and the alkylidene species with olefins, we propose that the K_{eq} of the equilibrium affects the product distribution (acyclic vs. cyclic enol ether).[47-49] When the dibromoalkane source used to generate **2.16** is unsubstituted, as in the case of dibromomethane, the equilibrium lies to the left favoring the formation of the mixed metalloid species **2.16**, and thus produces acyclic enol ether. However, when substitution is incorporated on the dibromoalkene source, such as dibromoethane, the mixed metalloid formation is disfavored, presumably due to steric interactions with ligands on Ti or through the stablization of the alkylidene thereby favoring titanium ethylidene formation **2.17** (Figure 2.12).[28]

The fact that cyclic material could be generated exclusively by utilizing a more substituted titanium alkylidene reagent was unprecedented. Dr. Karthik Iyer subseuentially investigated the scope of the reaction and has found it to be applicable to a broad range of substrates (Table 2.13).

We had previously examined the reaction of **2.9** with the titanium methylidene reagent and had found it to give a mixture of products (Figure 2.9).[30] However, when **2.9** was subjected to the titanium ethylidene reagent, we isolated cyclic enol ether **2.10** as the only identifiable product in 75% yield (entry 1). More challenging cyclization substrates that lacked a cyclic template were also subjected to the titanium ethylidene reagent (entries 2-4).[28] In all cases, only cyclic enol ethers were obtained in good yield.

Dr. Iyer's work has since led to the investigation of using the titanium ethylidene reagent to affect two-directional olefinic-ester metathesis. The idea was inspired by the symmetrical nature of the natural products and other efficient two-directional approaches that have been reported in the literature.[50-54]

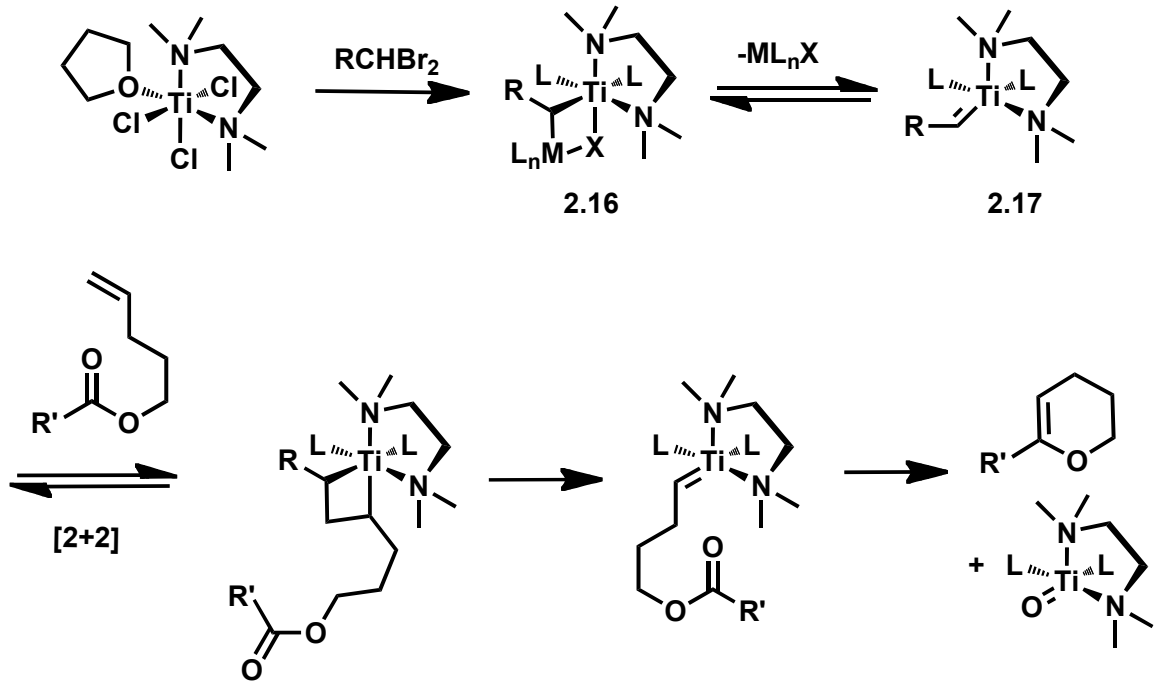
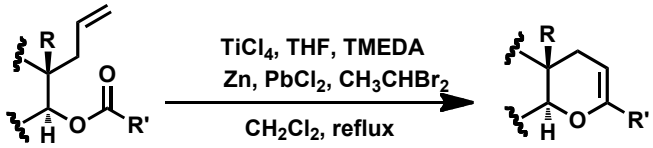


Figure 2.12. Mechanism of the olefinic-ester cyclization



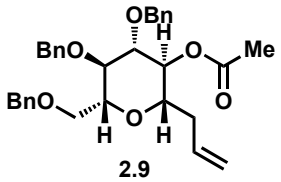
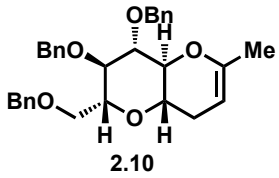
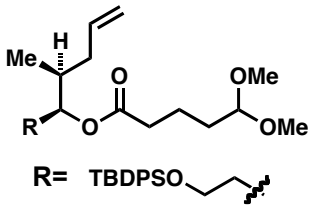
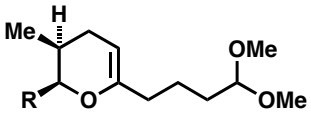
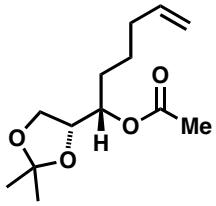
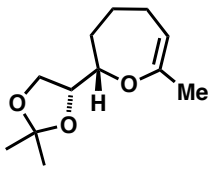
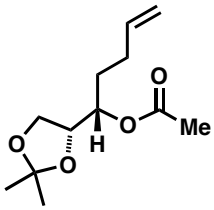
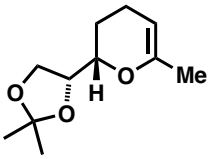
entry	starting material	cyclic enol ether	yield (cyclic:acyclic)
1	 2.9	 2.10	(75%, all cyclic)
2	 R= TBDPSO		(80%, all cyclic)
3			(75%, all cyclic)
4			(75%, all cyclic)

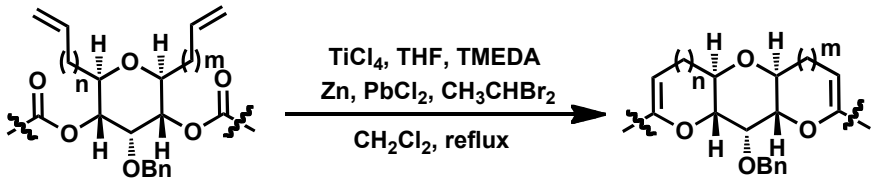
Table 2.13. Abbreviated list of olefinic-ester cyclizations using titanium ethylidene

Colleague Yuan Zhang found that use of the titanium ethylidene reagent allowed for the rapid construction of polycyclic ether natural products through utilization of substrates that allow for two enol ethers to be formed in a single flask from a bis-olefinic-ester.[55] As shown in Table 2.14, the method allowed rapid entry into polyether skeletons. Currently, colleague Dr. Xin Hao is using this transformation as a tool to synthesize *des*-methyl analogues of gamberiol (Figure 2.15).

After the development of the aforementioned olefinic-ester cyclizations, we became intrigued that the use of a reduced titanium reagent may also affect olefinic-amide cyclizations (Table 2.16). Precedent for this transformation was illustrated in Bennasar's work involving the initial conversion of amides into mixtures of cyclic and acyclic enamides using Tebbe's reagent.[56] The mixture was then converted into cyclic enamides using Grubbs' second generation catalyst. Using Bennasar's chemistry as impetus, colleague Dr. Jie Zhou found that the olefinic-amide cyclization was applicable to the synthesis of four- and six- membered enamines from the corresponding 3-substituted azepanones.[57] When Zhou employed different aromatic olefinic-lactam substrates, indole and dihydroquinoline skeletions were efficently formed (entries 3 and 4, respectively).

Results and Discussion

Combining our experience with olefinic-ester and olefinic-amide/lactam cyclizations we became interested in studying olefinic-lactone cyclizations. Described herein is the successful use of the titanium ethylidene reagent in this context.[29] We initially chose to examine the conversion of olefinic-lactone **2.18** to the corresponding



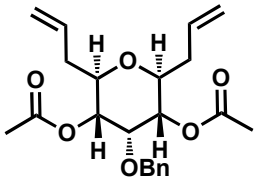
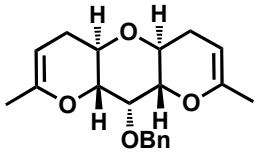
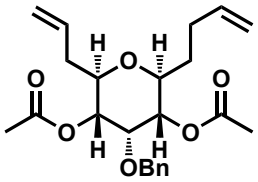
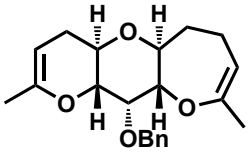
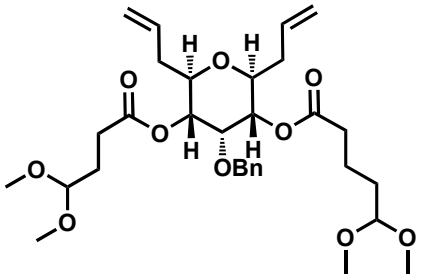
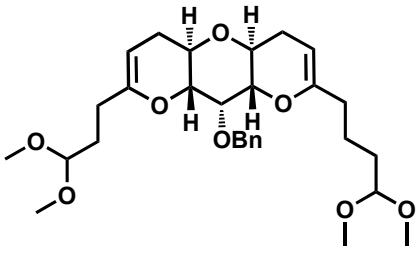
entry	starting material	cyclic enol ether	yield
1			65%
2			64%
3			60%

Table 2.14. Two-directional olefinic-ester cyclizations

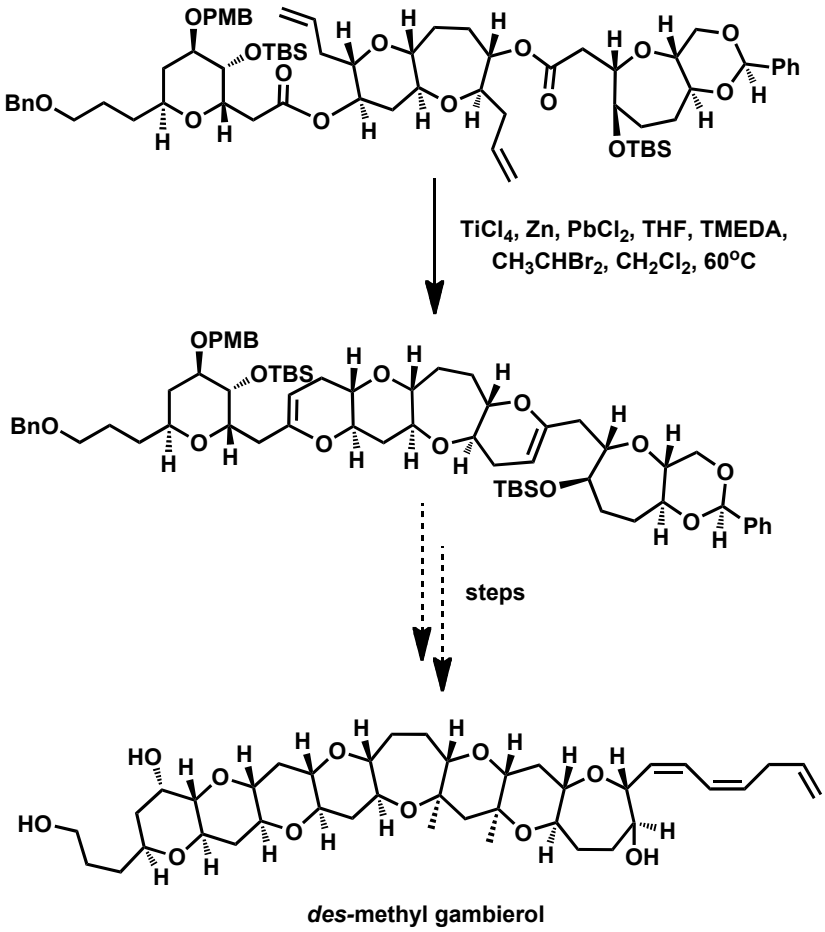
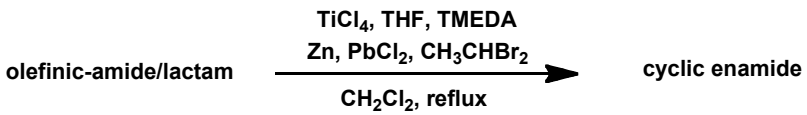


Figure 2.15. Two-directional approach to the synthesis of *des*-methyl gambierol



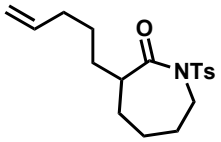
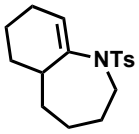
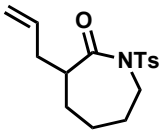
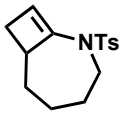
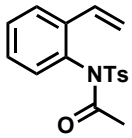
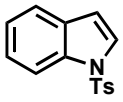
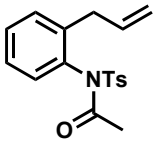
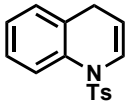
entry	olefinic-amide/lactam	cyclic enamide	yield
1			82%
2			70%
3			70%
4			78%

Table 2.16. Olefinic-amide cyclizations to enamides

ansa-dihydropyran macrolide **2.19** (Figure 2.17). The olefinic-lactone was generated in three steps from commercially available **2.20**. The conversion included oxidation, Grignard addition, and lactonization. To our delight, when **2.18** was subjected to the titanium ethylidene reagent, **2.19** was isolated as the sole product in quantitative yield. To the best of our knowledge, similar transformations have not been demonstrated prior to this work. Thus, we set out to investigate the scope of the reaction.

Various olefinic-lactones were synthesized with variation of the length of the olefin linker and lactone size (Figure 2.18). Rapid access to the cyclization precursors was necessary to be able to direct our focus to the olefinic-lactone cyclization. A variety of commercially available *seco*-acids with pendant primary alcohols could be oxidized to the aldehyde without the need to protect the carboxylic acid. Initially, we screened DMSO-mediated oxidations and found that the electrophilic intermediates produced in the reaction alkylated the carboxylic acid and led to undesired byproducts. We then chose to look at oxidations mediated by hypervalent iodine, namely Dess-Martin periodinane and iodoxybenzoic acid (IBX).[58] When employing the Dess-Martin reagent, conversions to the aldehyde were low, which is perhaps due to the limited solubility of the *seco*-acids in CH_2Cl_2. Alternatively, when IBX was used in the more polar solvent, DMSO, quantitative conversions to the aldehyde were observed. Once the reaction was complete, a simple aqueous workup provided the crude acid-aldehyde that was subjected to an excess of Grignard reagent to give the corresponding olefinic *seco*-acid **2.22**. The variation of the alkene linker length was achieved through the addition of either butenyl or pentenyl magnesium bromide to the aldehyde. The olefinic *seco*-acids were subjected to Yamaguchi macrolactonization conditions to give the corresponding 13- and 16-

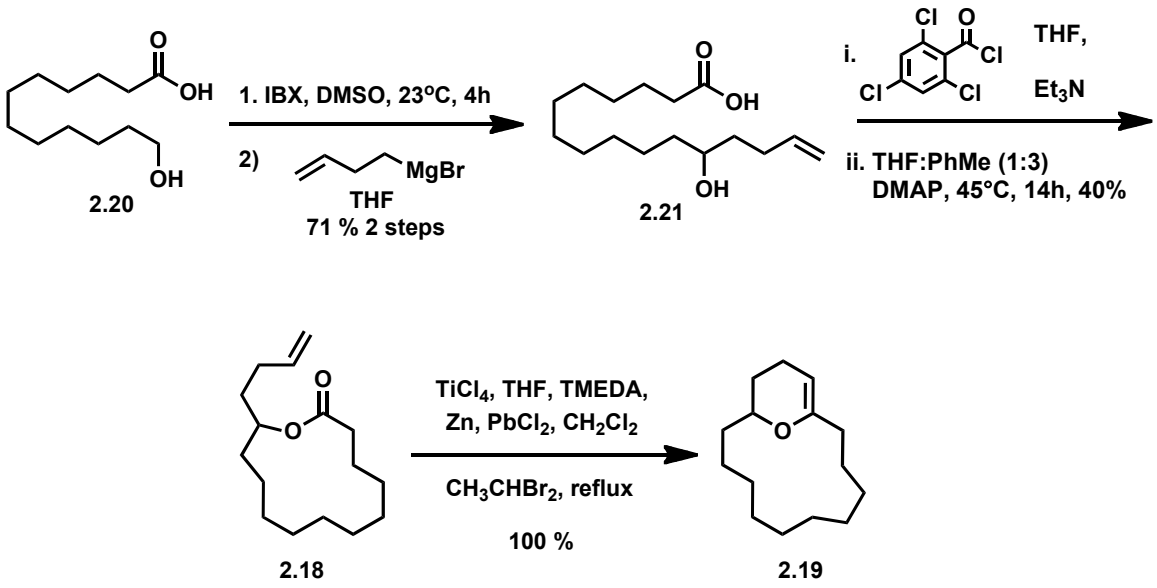


Figure 2.17. Synthesis of the 13 membered olefinic lactone **2.18** and its cyclization to **2.19**.

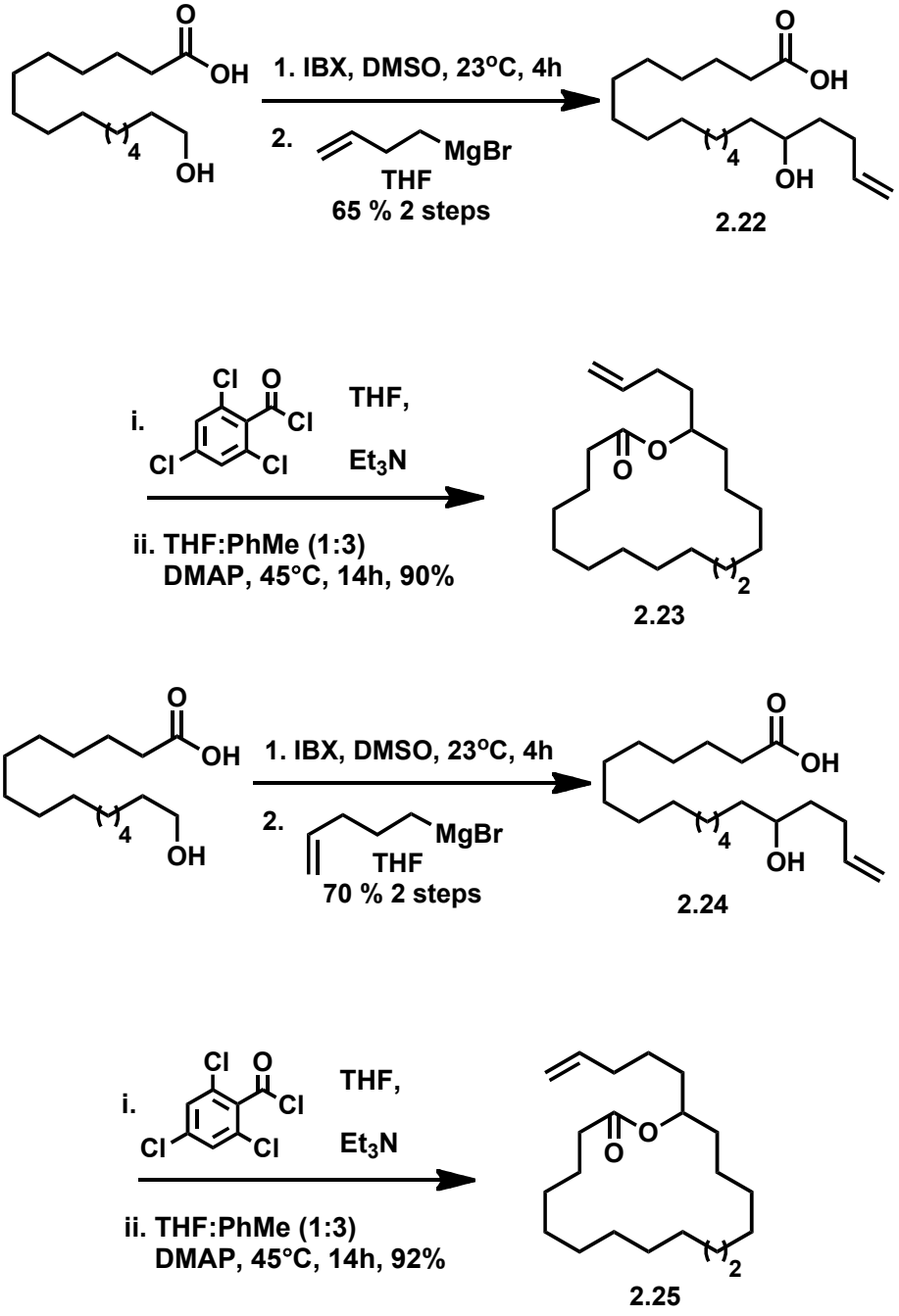


Figure 2.18. Synthesis of olefinic-lactone substrates

membered lactones.[59] High yields in the case of the 16-membered lactones (**2.23** and **2.25**) were obtained when the mixed anhydride was added over 12 hrs to a dilute solution of DMAP in toluene at 45°C.[60] Employing these same conditions, moderate macrolactonization yields were observed in the formation of the medium-sized 13-membered ring (Figure 2.17, **2.18**). This is likely due to ring strain as the corresponding dimer was observed as a byproduct.

We also decided to embed an amine in the macrocycle to see if the titanium ethylidene reagent would be compatible with a Lewis basic site within the substrate. Toward this end, we set out to synthesize the benzyl-amine containing substrate **2.30** (Figure 2.19).

The synthesis commenced with reductive amination between known aldehyde[61] **2.26** and amine **2.27** followed by TIPS deprotection and ester hydrolysis to give the *seco*-acid **2.29**. Yamaguchi macrolactonization provided the olefinic-lactone **2.30**. With the substrate syntheses complete, we investigated their cyclizations using the titanium ethylidene reagent.

We found that the scope was indeed general with respect to lactone size, as dihydropyran formation was successful with 16- membered lactones, **2.23** and **2.25** to give the 6-membered **2.31** and 7-membered **2.33** *ansa*-macrolides, respectively (Table 2.20). The benzylamine containing lactone **2.30** also underwent smooth conversion to **2.32** in 69% yield. Notably, in all cases, only cyclic material was obtained when the titanium ethylidene reagent was employed.

The enol ethers generated in these cyclization reactions are precursors to a number of interesting heterocyclic compounds. To demonstrate the amenability of the cyclization

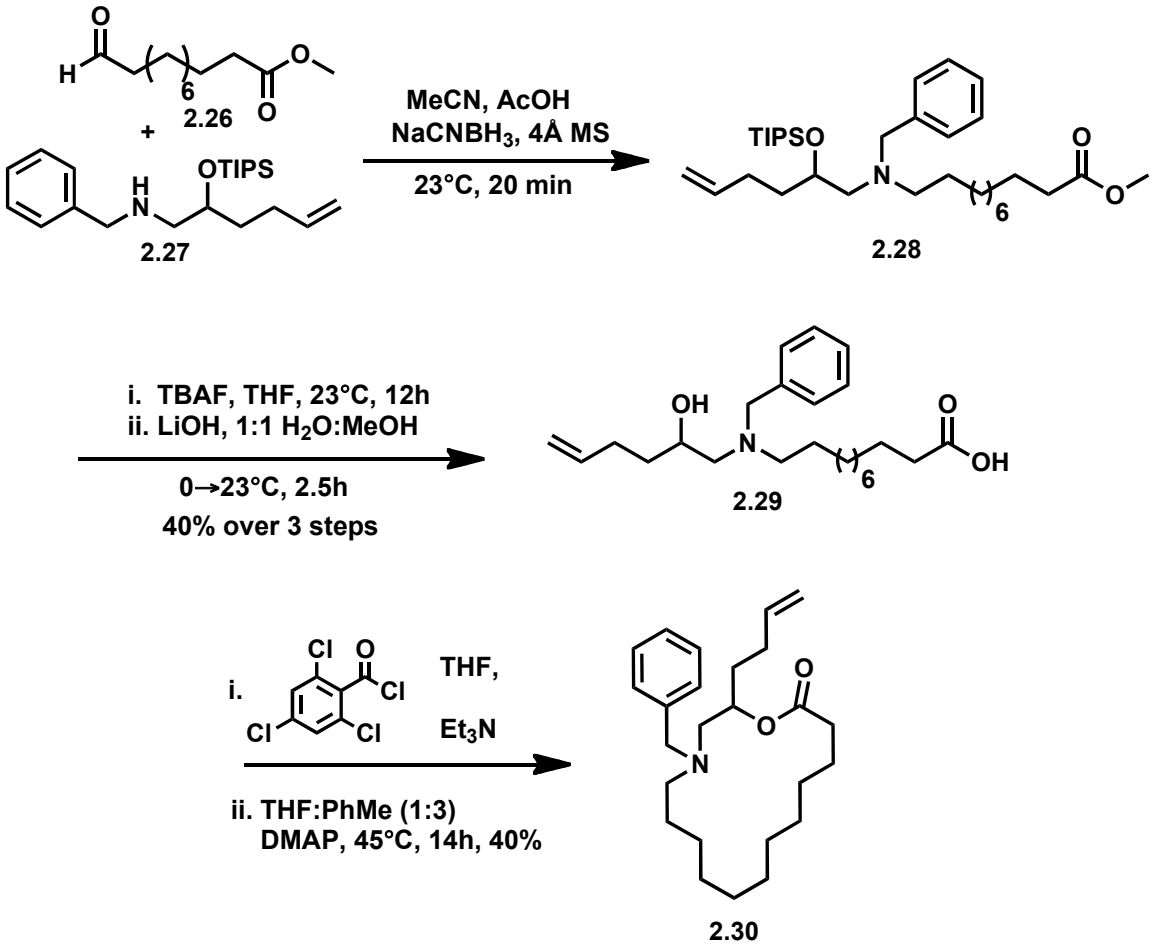
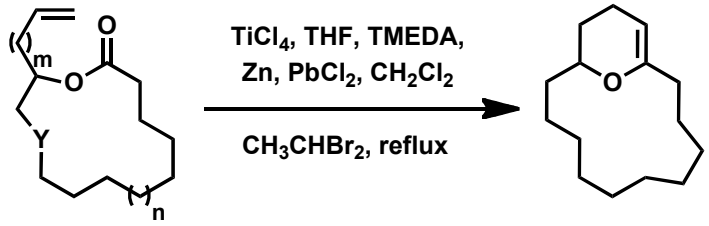


Figure 2.19. Synthesis of olefinic-lactone substrate **2.30**



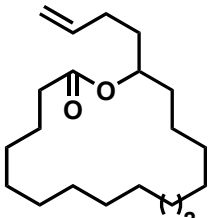
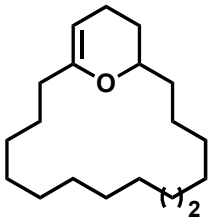
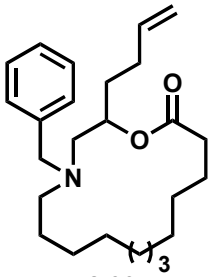
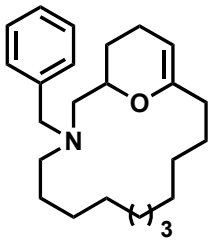
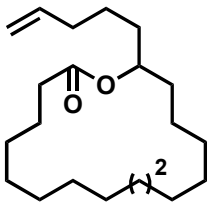
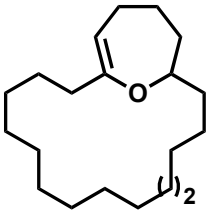
entry	lactone	cyclic enol ether	yield
1	 2.23	 2.31	87%
2	 2.30	 2.32	69%
3	 2.25	 2.33	78%

Table 2.20. Olefinic-lactone cyclizations to *ansa*-macrocyclic enol ethers

products towards the synthesis of more elaborate substrates, we decided to exploit the inherent reactivity of the enol ethers. With this in mind, hydrolysis of cyclic enol ether **2.31** with silica gel gave the ring-expanded all-carbon macrocycle (Figure 2.21). The resulting hydroxyketone was then treated with benzoic anhydride and the resulting ester **2.34** was isolated in 63% yield from lactone **2.23**. Alternativly, **2.31** was then treated with *m*CPBA in anhydrous MeOH to give mixed ketal **2.35** in 68% yield.[38] Lastly, reduction of the enol ether using Et_3SiH and TFA produced the σ_v symmetric pyran **2.36** as a single diasteromer.

As a further illustration of the utility of this method, we applied the lactone formation/reduced Ti mediated cyclization/ring expansion sequence to the synthesis of the natural products (*R*)-(-)-muscone and (*R*)-(+)-muscopyridine.[29]

Synthesis of (*R*)-(-)-muscone and (*R*)-(+)-muscopyridine

The organic compound primarily responsible for the characteristic odor of musk is muscone and may be obtained naturally from the glandular secretions of the male musk deer (*Moschus moschiferus*) that is native to central Asia.[62] The odoriferous secretion functions as a sex pheromone for the deer and is one of the oldest-known ingredients of perfumes. Harvesting the secretions results in the death of the animal and, because of muscone's large demand, the musk deer population diminished leading to their classification as "endangered".[62] Synthetic production of muscone became an attractive solution that could prevent the extinction of the musk deer and provide unliminted quantities of muscone. One method, common to the perfumery industry for the synthesis of muscone takes advantage of the fact that aldol condensations are among the least

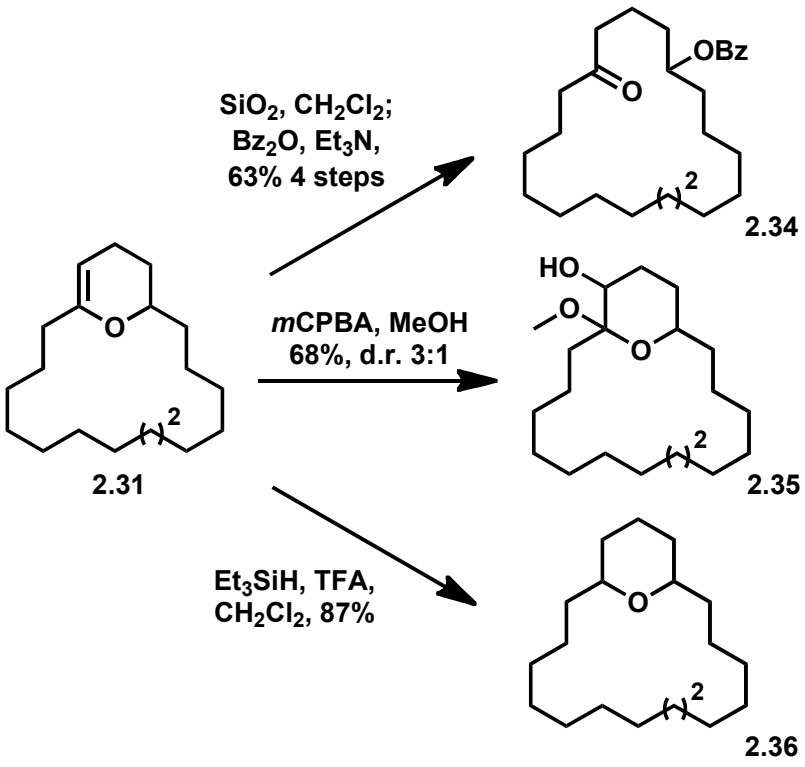


Figure 2.21. Reactions of enol ether **2.27** to provide various macrocycles.

expensive method of C-C bond formation.[63, 64] The gas phase intramolecular aldol reaction of 2,15-hexadecadione **2.37** using metal oxides as catalysts is an efficient, cheap method to produce racemic muscone (Figure 2.22).[63] The racemic muscone differs only slightly in scent, having a slightly lower odor threshold than the enantiopure material.[62] Most syntheses of optically active muscone involve RCM or RCAM that require high dilutions, which is impractical for industral production.[63,65,66]

Another unique synthesis of *rac*-muscone was completed by Eschenmoser and coworkers and employs the Eschenmoser fragmentation reaction was a key step (Figure 2.2).[67] The synthesis commences with the epoxidation of bicyclic ketone **2.39** with hydrogen peroxide under basic conditions, followed by addition of methane sulfonylhydrazine to the ketone to generate hydrazone **2.40**. The Eschenmoser fragmentation is then initiated through the deprotonation of the hydrazone to generate alkyne **2.41** and N_2. The alkyne **2.41** was easily reduced to produce *rac*-muscone. Eschenmoser's oxidation/ring-expansion strategy as a means to produce the all-carbon macrocyclic ring is conceptually similar to our own work as outlined below (Figure 2.23 and 2.24).

Our method utilizes an olefinic-lactone cyclization/ring expansion method towards the synthesis of muscone and its cognate natural product, muscopyridine. Our synthesis of both molecules began from aldehyde **2.42** which was subjected to the Horner-Wadsworth-Emmons (HWE) reagent derived from (*R*)-phenylglycine **2.43**. The HWE reagent was prepared from the corresponding bromoacetyl oxizolidone through a Michaelis-Arbuzov reaction using triethylphosphite.[68] The HWE reaction served to homologate the alkyl chain while simultanously introducing the (*R*)-phenylglycine-

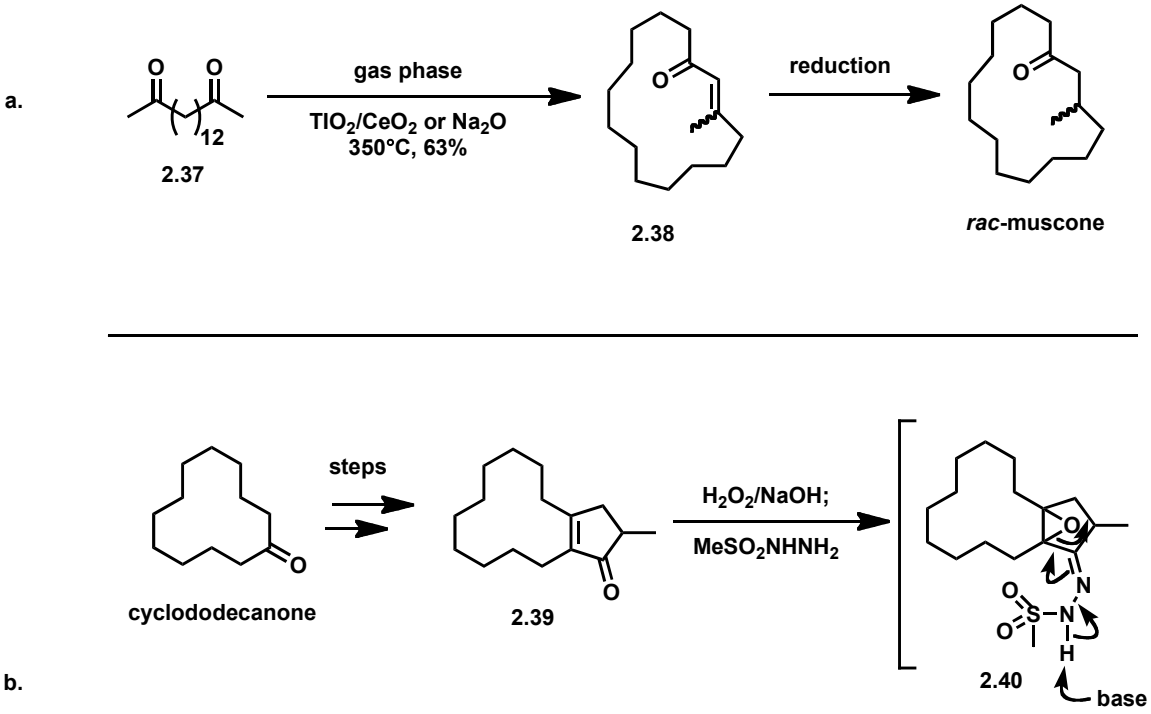


Figure 2.22. Synthesis of muscone via: a. intramolecular aldol; b. Eschenmoser fragmentation

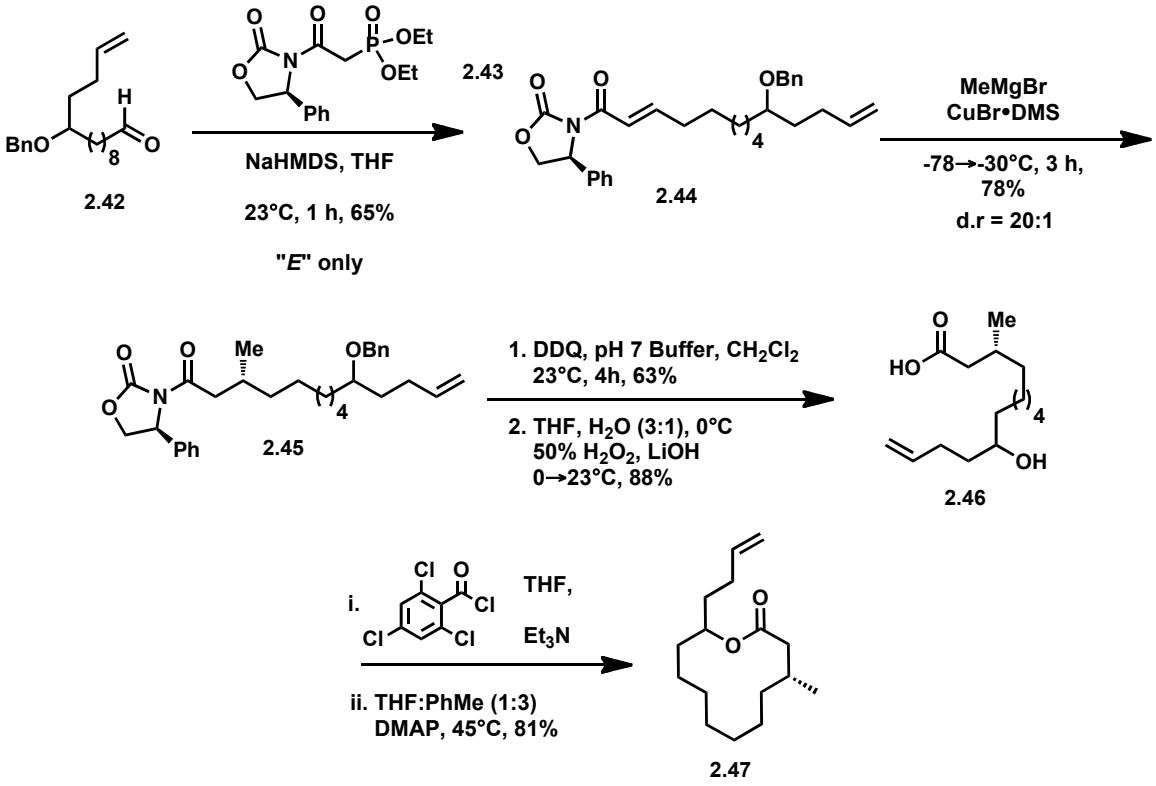


Figure 2.23. Synthesis of the muscone and muscopyridine precursor olefinic-lactone **2.47**

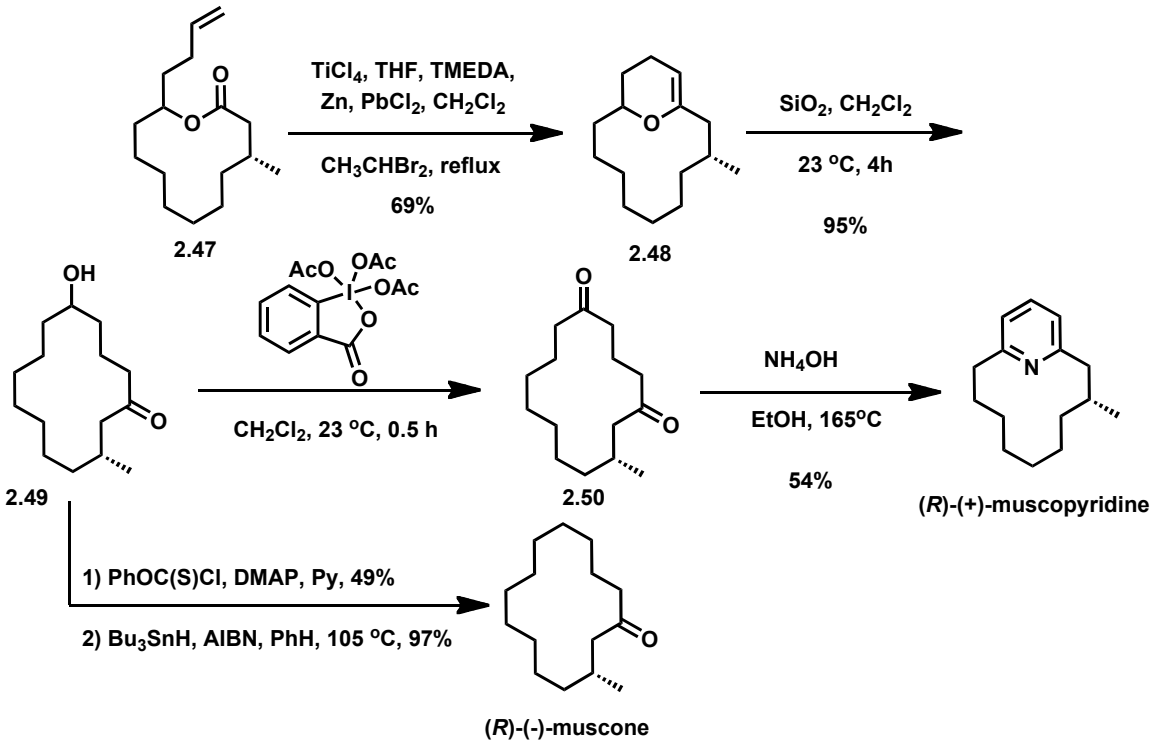


Figure 2.24. Completion of the synthesis of muscone and muscopyridine

derived auxiliary required for the asymmetric Michael addition. Methyl cuprate addition to unsaturated oxazolidinone **2.44** using Hruby's method proceeded smoothly to give **2.45** as essentially a single diasteriomer (d.r. > 20:1) in 69% yield.[69] Oxidative removal of the benzyl group using DDQ gave the corresponding secondary alcohol. Liberation of the acid through hydrolysis of the oxazolidinone produced olefinic *seco*-acid **2.46**. Yamaguchi macrolactonization of **2.46** gave 13-membered olefinic-lactone cyclization precursor **2.47** in good yield. The dihydropyran **2.48** was smoothly formed upon the subjection of **2.47** to the titanium ethylidene reagent. Ring expansion of the macrocyclic dihydropyran **2.48** using silica gel gave the hydroxyketone **2.49**, which served as a precursor to both muscone and muscopyridine. (*R*)-(-)-Muscone was synthesized through a Barton-McCombie deoxygenation of **2.49**, whereas (*R*)-(+)-muscopyridine resulted from the oxidation of the secondary alcohol in **2.49** to give the diketone **2.50**.[70] The diketone was subjected to pyridine formation conditions that employ hydroxylamine hydrochloride in ethanol at 165 ^{0}C to give (*R*)-(+)-muscopyridine.[71] Spectral data of (*R*)-(-)-Muscone and (*R*)-(+)-muscopyridine matched in all respects with that of literature reported samples.[66,71] In summary, we have described a unique and efficient approach to all-carbon macrocycles that utilizes an olefinic-lactone cyclization reaction as the key step. Application of our method to the synthesis of the natural products (*R*)-(-)-muscone and (*R*)-(+)-muscopyridine has been achieved.

Conclusion

In continuation of our study of the scope of this reaction, we plan on utilizing the olefinic-lactone cyclization to expedite the synthesis of polycyclic ether analogues. Our current strategy to synthesize the 6, 7- bicycle **2.58** that is common to hemibrevetoxin B

and gambierol syntheses involves 18 steps from commercially available D-glyderaldehyde.[31,39,40] It is believed that the synthesis can be shortened to 9 steps by employing an olefinic-lactone cyclization as shown in Figure 2.25. The second-generation approach would commence with the synthesis of key intermediate, hemiketal **2.52** that is believed to be available from cyclohexenone **2.51** in three steps using known chemistry.[72] A Grob-type fragmentation of **2.52** using hypervalent iodine is expected to generate the olefinic-lactone **2.53** that contains a "*Z*" olefin. Olefinic-lactone cyclization gives the *ansa*-dihydropyran **2.54** to which a selective DMDO epoxidation/$AlMe_3$ addition would be carried out to give **2.55**. Ozonylitic cleavage of the olefin is expected to deliver dialdehyde **2.56**. The dialdehyde would then be subjected to an acid mediated cyclization/elimination to provide oxepene **2.57** after olefination. Another DMDO oxidation/allyl Gringard addition would provide the desired the 6,7- bicycle **2.58**.

Alkyne-Ester Cyclizations

In addition to olefinic-lactone and olefinic-amide cyclizations, we sought to investigate the synthesis of tetra-substituted enol ethers through alkyne-ester metathesis. The formation of tetra-substituted enol ethers from the corresponding acyclic enol ethers using Grubbs' catalyst is a significant challenge to our group and others. Even

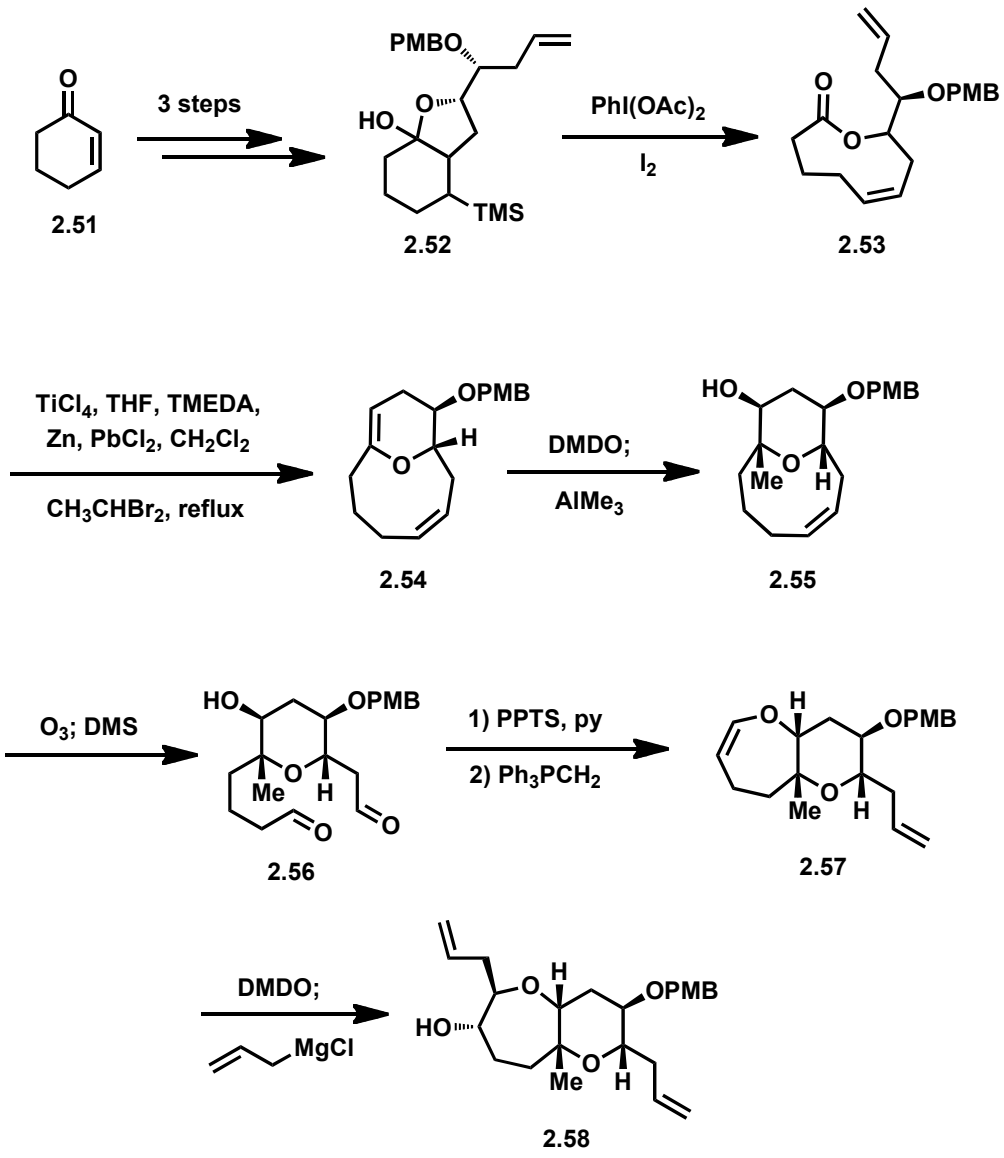
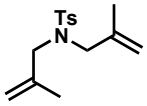
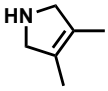
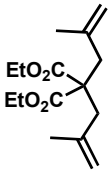
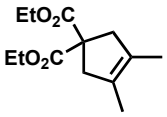
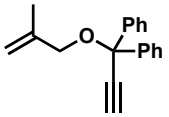
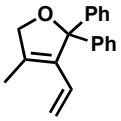


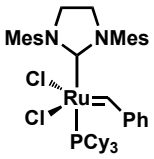
Figure 2.25. Potential application of the olefinic-lactone methodology to the synthesis of polycyclic ethers

the formation of tetrasubstituted olefins using Grubbs-type complexes is challenging (Table 2.26).[73,74] The conversions of entries 1-3 were low when the RCM was carried out using either Grubbs' second generation or the Hoveyda-Grubbs' catalysts.[74] In addition to the low yields from these transformations, the prolonged reaction times at high temperatures leads to decomposition of the catalyst.[74]

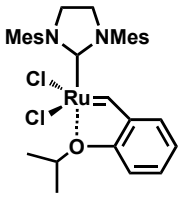
In contrast to these results, ene-yne metatesis that utilizes a platinum (II) species to generate tetrasubstituted enol ethers is efficient.[78] Enyne metathesis is a bond reorganization of an alkene and an alkyne to produce a 1,3-diene (Figure 2.27). Mechanisitic work by Furstner and coworkers showed that activation of the alkyne by Pt(II) coordination leads to oxonium ion formation, which results in the release of the allyl carbocation.[78,79] Allyltransfer to the electron rich carbon-platinum bond generates the tetrasubstituted enol ether. The yields are generally good for these types of reactions, however *E,Z* mixtures that result from non selective allyl transfer to the cationic intermediate typically occur. In the examples shown in Table 2.27, a single alkene isomer was produced.

Similar to these results, if alkyne-ester cyclizations were successful they would also generate a tetra-substuted enol ether. Utilizing the titanium ethylidene reagent would be substantially cheaper than Grubbs' catalyst, it may be generated in situ and exhibits lower Lewis acidity relative to other titanium alkylidenes. In addition to the tetra-substituted olefin that would result from an alkynyl-ester cyclization, a 1,3-diene would also be formed from the reaction. We believed the generation of the tetrasubstituted olefins would be driven by the enthalpic stability of the conjugated 1,3-diene. In any instances, we felt that because alkyne-carbonyl metathesis is unprecedented it warranted

entry	subsrate	product	cat. (5 mol%), yield
1	 2.59	 2.62	G2: 52% H-G: 45%
2	 2.60	 2.63	G2: 14% H-G: 2%
3	 2.61	 2.64	G2: 20% H-G: 7%



Grubbs 2nd generation catalyst (G2)



Hoveyda-Grubbs Catalyst (H-G)

Table 2.26. Generation of cyclic tetrasubstituted olefins using Grubbs' second generation and Hoveyda-Grubbs catalysts.

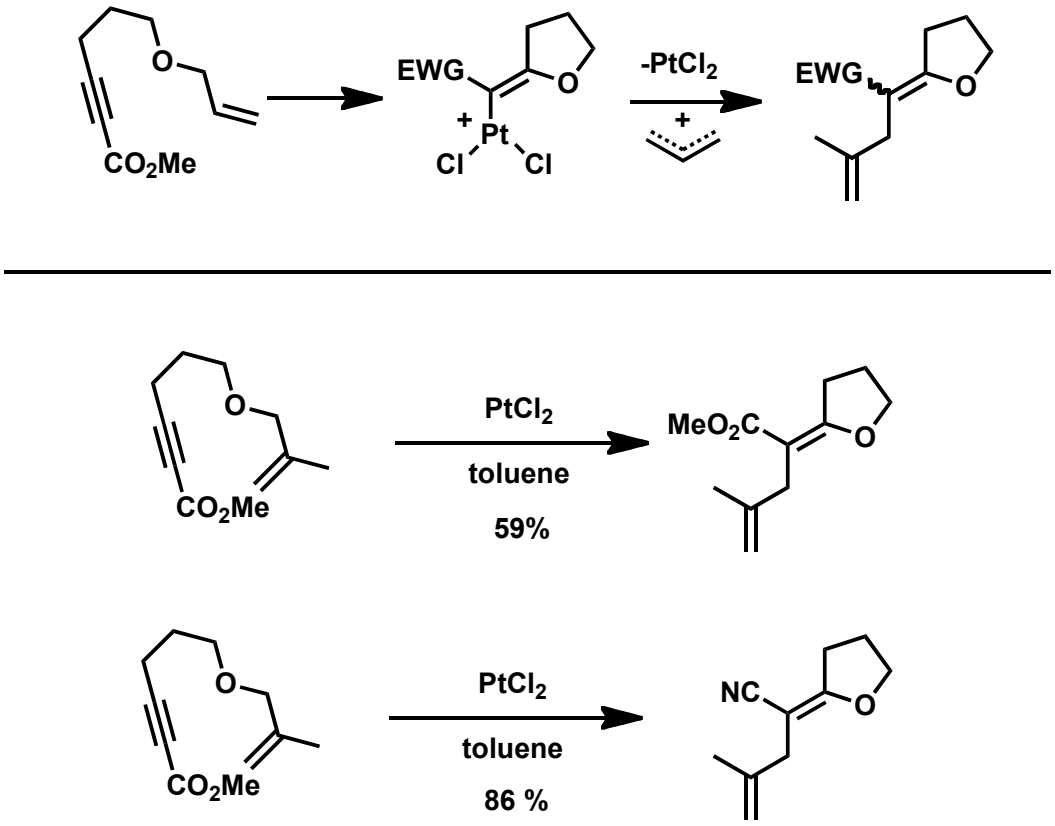


Table 2.27. Eyne metathesis using $PtCl_2$ to generate tetrasubstituted enol ethers.

further investigation.

Various alkynyl-ester substrates were synthesized that included both cyclic and acyclic templates. We were able to rapidly access cyclization precursors **2.67** and **2.70** though chemistry that has been previously established in our laboratories from the known D-glucal derived starting materials **2.65** and **2.68**, respectively (Figure 2.28).[30] After oxidation of **2.65** with dimethyl dioxirane (DMDO) to generate the corresponding epoxide, propargyl magnesium bromide was added to achieve carbon-carbon bond formation that led to exclusive formation of the β-*C*-glycoside **2.66** in 72% yield. The secondary alcohol of **2.66** was subsequently acylated to give cyclization precursor **2.67**. The synthesis of **2.70** proceeded in an analogous fashion from **2.68**. In addition to the propargyl β-*C*-glycosides **2.67** and **2.70** we thought that the substrate scope should contain an acyclic template alkynyl-ester and **2.73** was prepared from known aldehyde **2.71**[28] through a Grignard addition of the homo-propargyl species **2.72**[77] followed by TMS cleavage and acylation of the secondary alcohol.

With the substrates in hand, we initially turned our attention to their cyclization using the titanium ethylidene reagent derived from dibromoethane (Table 2.29). When **2.67** was subjected to these conditions, we isolated a complicated mixture of products. Crude ^{1}H NMR analysis indicated that the desired product was formed, however a significant amount of unidentified byproducts were present, which we were unable to separate via chromatography. In addition, the crude yield was low. Similar results were obtained when **2.70** was subjected to the titanium ethylidene reagent.

When the more challenging alkyne-ester substrate **2.73** was employed complete decomposition of the starting material was observed. Discouraged by these results, we

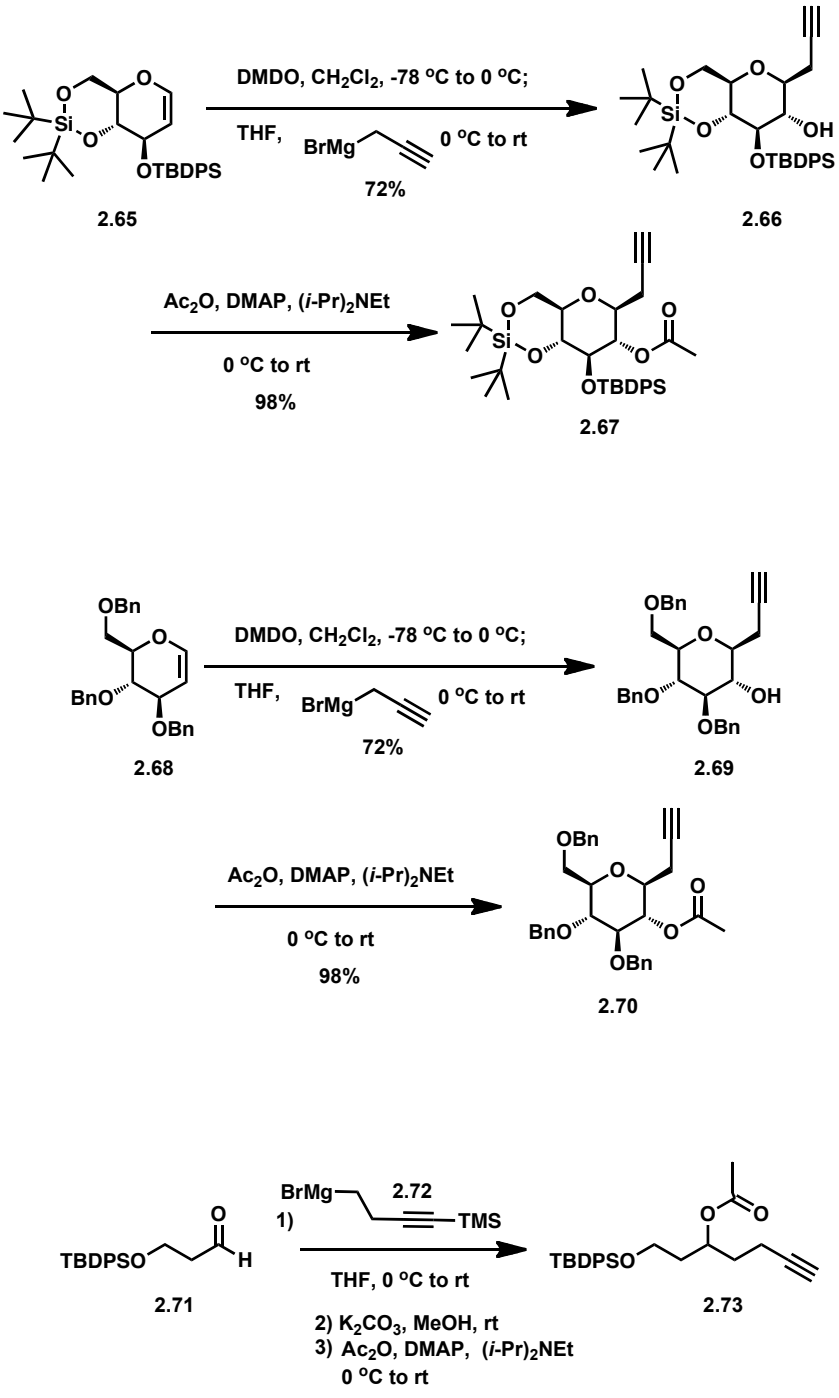
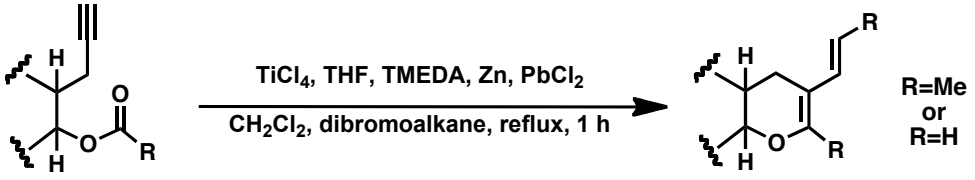


Figure 2.28. Synthesis of substrates **2.67**, **2.70**, and **2.73**.



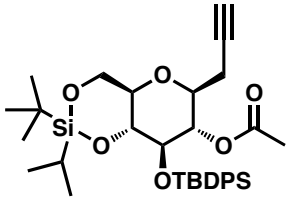
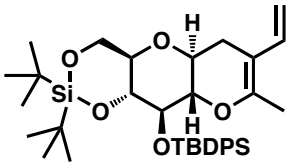
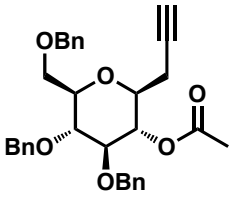
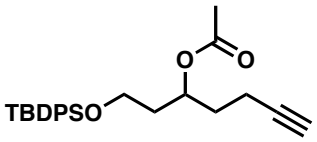
Entry	Starting Material	Dibromoalkane	1,3-diene	Yield
1)	 2.67	CH_3CHBr_2	complicated mixture of products	
2)	2.67	CH_2Br_2	 2.74	63%
3)	 2.70	CH_3CHBr_2	complicated mixture of products	
4)	2.70	CH_2Br_2	complicated mixture of products	
5)	 2.73	CH_3CHBr_2	complicated mixture of products	
6)	2.73	CH_2Br_2	complicated mixture of products	

Table 2.29. Alkynyl-ester metathesis.

elected to employ a titanium methylidene reagent to affect alkynyl-ester cyclization of the hindered substrate **2.67**. Previous studies in our group indicated that the titanium methylidene reagent was able to affect olefinic-ester cyclizations when the ester was hindered.[46] Using these results as impetus, we subjected substrate **2.67** to the titanium methylidene reagent and were delighted to isolate the tetrasubstituted enol ether **2.74** in 63% yield. This preliminary result indicated that the titanium-methylidene reagent could indeed induce alkyne-ester metathesis.

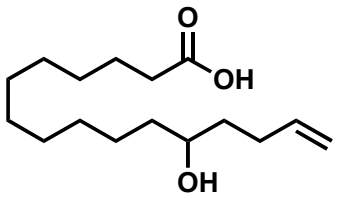
To our knowledge, we have demonstrated the first alkyne-ester metathesis reaction. The results indicate that optimization is required to fully realize the potential of this unique transformation. Advancement in alkynyl-ester metathesis might include the determination of the byproducts, which were formed in the above reactions; as this may provide insight as to what the problem of the reaction may be. Also, a better understanding of the titanium ethylidene reagent would likely facilitate its optimization. Optimization might include the exploration of ligand substitution on the mixed metalloid species that leads to the alkylidene species. For example, we could investigate the use of different amines other than tetramethylethylenediamine: perhaps by changing the sterics about the titanium reagent, we can tune its reactivity for optimization. Also, the affect of leaving groups other than 1,1-dibromides will be examined in hopes to better understand the reactivity of the titanium alkylidene species.

Supporting Information

General Experimental Procedures

Unless otherwise noted, all reactions were performed under a nitrogen atmosphere in

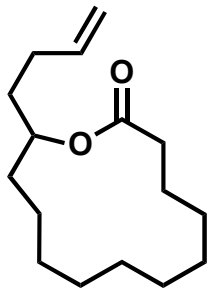
flame-dried glassware. NMR spectra were recorded on a Varian VXR-500 MHz spectrometer. Chemical shifts were reported in δ, parts per million (ppm), relative to benzene (7.16), dichloromethane (5.32) or chloroform (7.27) as internal standards. Coupling constants, *J*, were reported in Hertz (Hz) and refer to apparent peak multiplicities. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer. Mass spectra were recorded at the Mass Spectrometry Facility at the Department of Chemistry of the University of Utah at Salt Lake City on a Finnigan MAT 95 mass spectrometer. Dichloromethane, TMEDA and pyridine were dried by distillation from calcium hydride and saturated with nitrogen. Tetrahydrofuran and diethyl ether were dried from the sodium ketyl of benzophenone and distilled before use. Zinc dust (<10 μm, Aldrich) was activated by washing with 5% hydrochloric acid, H_2O, ether, and acetone and dried *in vacuo* overnight. The activated zinc was stored under nitrogen in a dessicator. All other reagents were used without further purification unless otherwise noted. Analytical thin–layer chromatography (TLC) was performed on silica gel plates (0.25 mm) precoated with a fluorescent indicator. Flash chromatography was performed using 40–63 μm silica gel (200 X 400 mesh).



12-hydroxyhexadec-15-enoic acid (2.21). To a solution of 12-hydroxydodecanoic acid (0.220 g, 1.01 mmol) in DMSO (2.20 mL) at rt was added IBX (0.340 g, 1.21 mmol). After stirring for 4 h the reaction mixture was diluted with ether (50 mL) and the reaction was quenched with H_2O (20 mL). The organic phase was washed with H_2O (2 x 20 mL),

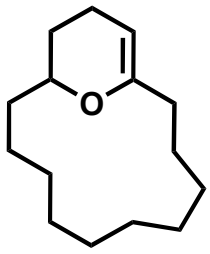
dried ($MgSO_4$), and concentrated to afford the corresponding aldehyde (12-oxododecanoic acid) as a white solid. The aldehyde was used in the next reaction without additional purification.

A solution of 4-bromo-1-butene (1.01 mL, 10.0 mmol) in THF (10 mL) was added to Mg turnings (0.680 g, 20.0 mmol) over 1 h at rt. The slurry was allowed to stir for an additional hour before being transferred to a solution of the crude aldehyde from above (1.01 mmol) in THF (4.6 mL) at 0 °C. After 1 h the reaction was quenched with sat. NH4Cl (aq., 10 mL) and the resulting mixture diluted with Et_2O (50 mL). The organic phase was washed with brine (50 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes:ethyl acetates, 10:1 to 5:1 to 1:1) gave 195 mg of *seco*-acid **2.21** (71%) as a white, waxy solid. mp 40-41 °C; R*f* = 0.32 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 16.9, 10.1, 6.6, 6.6 Hz, 1H), 5.03 (ddd, *J* = 17.2, 3.6, 1.6 1H), 4.96 (dddd, *J* = 10.1, 2.0, 1.3, 1.3 Hz, 1H), 3.66-3.60 (m, 1H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.25-2.06 (m, 2H), 1.66-1.27 (m, 22 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 138.8, 114.9, 71.8, 37.5, 36.5, 34.3, 30.2, 29.8, 29.7, 29.6, 29.5, 29.3, 29.2, 25.7, 24.9; IR (neat) 3500-2500 (broad), 2918, 2850, 1696, 1465, 1440, 1249, 1217, 1120 cm^{-1}; LRMS *m/z* calcd for $C_{16}H_{31}O_3$ $(MH)^+$ 271.1, found: 271.0.



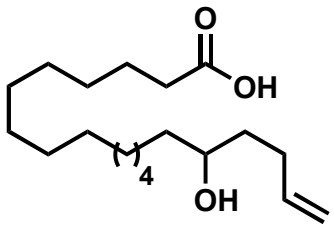
13-(but-3-enyl)oxacyclotridecan-2-one (2.18). To a solution of *seco*-acid **2.21** (0.100 g, 0.369 mmol) in THF (3.70 mL) at rt were sequentially added Et_3N (0.056 mL, 0.40

mmol) and 2,4,5-trichlorobenzoyl chloride (0.057 mL, 0.37 mmol). After 5.5 h, the reaction mixture was diluted with toluene (185 mL) and transferred over a period of 6 h to a solution of DMAP (0.271 g, 2.22 mmol) in toluene (37 mL) at 48 ºC. After the addition was completed the reaction mixture was stirred for an additional 2 h after which it was cooled to rt and concentrated. Flash chromatography (hexanes:ethyl acetate, 100:1 to 50:1) gave 70 mg of macrolactone **2.18** (75 %) as a brown oil. R*f* 0.63 (10:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (dddd, *J* = 16.8, 10.2, 6.6, 6.6 Hz, 1H), 5.02 (ddd (*J* = 17.2, 3.4, 1.8 Hz, 1 H), 4.98-4.93 (m, 2H), 2.44 (ddd, *J* = 13.9, 8.4, 3.5 Hz, 1H), 2.26 (ddd, *J* = 13.8, 9.4, 3.5 Hz, 1H), 2.10-2.04 (m, 2 H), 1.76-1.53 (m, 6 H), 1.47-1.26 (m, 14 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 138.2, 115.0, 74.1, 35.2, 34.2, 33.5, 30.0, 27.0, 26.6, 26.2, 25.2, 25.0, 24.8, 24.7, 22.8. IR (neat) 2931, 2860, 1731, 1447, 1249, 1099 cm^{-1}; LRMS *m/z* calcd for $C_{16}H_{28}O_2(MH)^+$ 253.2, found: 253.1.



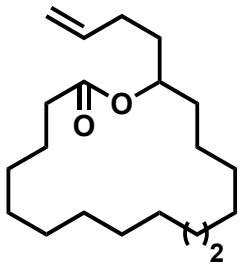
16-oxabicyclo[10.3.1]hexadec-12-ene (2.19). $TiCl_4$ (0.31 mL, 2.8 mmol) was added to CH_2Cl_2 (10 mL) at 0 °C. To the resulting solution was sequentially added THF (1.2 mL, 14 mmol) and TMEDA (2.06 mL, 13.7 mmol) dropwise. The ice bath was removed and the mixture was allowed to stir for 20 min. Activated Zn dust (0.333 g, 5.13 mmol) and $PbCl_2$ (0.075 g, 0.27 mmol) were added at once. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3-5 min. To the blue-green slurry was added a solution of macrolactone **2.18**

(0.018 g, 0.071 mmol) and CH_3CHBr_2 (0.20 mL, 2.3 mmol) in CH_2Cl_2 (1 mL + 1 mL rinse). The reaction mixture was then heated at 65°C for 2 h, cooled to 0 °C, and the reaction was quenched with sat. K_2CO_3 (aq., 2 mL). After stirring for 0.5 h at 0 °C, the resulting mixture was filtered (1:1 hexanes:EtOAc) and the filtrate was concentrated. The residue was taken up in EtOAc and to this was added SiO_2 (ca 0.250 g). After concentration the resulting solid was loaded onto a silica gel column and eluted with hexanes:ethyl acetate (100:1 to 20:1) to give 13 mg of cyclic enol ether **6** (87%) as a clear yellow oil. R*f* 0.85 (10:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (m, 1H), 3.86-3.81 (m, 1H), 2.26-2.16 (m, 4 H), 2.10-2.02 (m, 2 H), 2.00-1.93 (m, 2H), 1.82-1.62 (m, 16 H); ^{13}C NMR (125 MHz, C_6D_6) δ 155.5, 95.7, 74.8, 34.3, 34.0, 30.5, 28.4, 27.3, 27.3, 27.2, 26.7, 26.5, 25.7, 23.6, 21.1; IR (neat) 3061, 2928, 2858, 1674, 1463, 1261, 1092, 1023 cm^{-1}; LRMS *m/z* calcd for $C_{15}H_{27}O$ $(MH)^+$ 223.2, found 223.3.

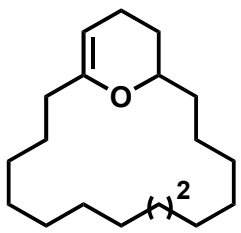


16-hydroxyicos-19-enoic acid. (2.20) Prepared according the general procedure described above for the preparation of **2.21** using 16-hydroxyhexadecanoic acid (0.300 g, 1.10 mmol), DMSO (2.2 mL), IBX (0.340 g, 1.21 mmol), and butenyl magnesium bromide (12 mL of a 0.83 M solution in THF, 10 mmol) to give 233 mg of *seco*-acid **2.20** (65%) as a white, waxy solid. mp 57-61 °C; R*f* = 0.45 (1:1 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.0, 10.3, 6.6, 6.6 Hz, 1H), 5.05-4.99 (m, 1H), 4.98-4.94 (m, 1 H), 3.64-3.59 (m, 1H), 2.35 (t, *J* = 7.4 Hz, 2 H), 2.12-2.04 (m, 2 H), 1.64 (pentuplet, *J* = 7.5 Hz, 2H), 1.61-1.26 (m, 26 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.0,

138.9, 114.9, 71.8, 37.7, 36.7, 34.3, 34.1, 30.3, 29.9, 29.8, 29.8, 29.7, 29.6, 29.4, 29.2, 29.2, 25.8, 25.5, 24.9 MHz; IR (neat) 3400-2600 (broad), 2917, 2849, 1700, 1433, 1261, 911 cm^{-1}; LRMS *m/z* calcd for $C_{20}H_{37}O_3$ $(M\text{-}H^+)^-$ 325.3, found: 325.4.

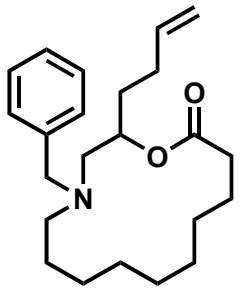


17-(but-3-enyl)oxacycloheptadecan-2-one, (2.23). Prepared according to the general procedure using *seco*-acid **2.22** (67 mg, 0.22 mmol) in THF (7.3 mL) and Et_3N (0.080 mL, 0.57 mmol), 2,4,5-trichlorobenzoyl chloride (0.045 mL, 0.28 mmol), toluene and THF (3:1, 50 mL), and a solution of DMAP (532 mg, 4.36 mmol) and toluene (120 mL) to give 60 mg of macrolactone **2.22** (90%) as a clear colorless oil. R*f* 0.20 (50:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 5.80 (dddd, *J* = 16.6, 10.3, 6.4, 6.4 Hz, 1H), 5.01 (ddd, *J* = 17.1, 3.0, 1.5 Hz, 1 H), 4.98-4.94 (m, 2 H), 2.37-2.27 (m, 2H), 2.09-2.02 (m, 2H), 1.75-1.52 (m, 6 H), 1.36-1.26 (m, 22 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 138.2, 115.0, 73.7, 34.9, 34.6, 34.0, 30.0, 28.5, 28.5, 28.4, 27.9, 27.8, 27.1, 27.1, 27.1, 26.8, 25.2, 24.8; IR (neat) 2928, 2857, 1734, 1458, 1109 cm^{-1}; LRMS *m/z* calcd for $C_{20}H_{36}O_2$ 309.3 $(MH)^+$, found 309.3.



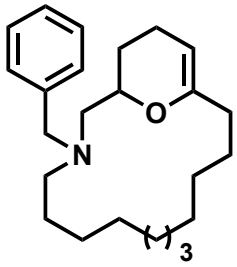
Oxabicyclo[14.3.1]icos-1(19)-ene, (2.31). Prepared according to the general procedure as described for the preparation of **2.19** using CH_2Cl_2 (12.5 mL), $TiCl_4$ (0.31 mL, 2.8

mmol), THF (1.5 mL, 17 mmol), TMEDA (2.6 mL, 17 mmol), activated Zn dust (0.41 g, 6.3 mmol), $PbCl_2$ (0.092 g, 0.33 mmol), and a solution of macrolactone **2.23** (0.027 g, 0.087 mmol) and CH_3CHBr_2 (0.25 mL, 2.8 mmol) in CH_2Cl_2 (1.2 mL + 1.2 mL rinse) to give 20. mg of cyclic enol ether **2.31** (83%) as a clear yellow oil. ^{1}H NMR (500 MHz, C_6D_6) δ 4.52 (dd, *J* = 4.0, 3.4 Hz, 1H), 3.70 (dddd, *J* = 8.8, 8.8, 2.9, 2.9 Hz, 1 H), 2.16-2.05 (m, 2H), 2.03-1.95 (m, 2H), 1.91-1.85 (m, 2H), 1.63-1.30 (m, 26H); ^{13}C NMR (125 MHz, C_6D_6) δ 155.3, 95.3, 75.4, 35.8, 35.5, 29.1, 28.6, 28.7, 28.1, 28.1, 28.0, 27.9, 27.7, 27.6, 25.6, 21.2; IR (neat) 2926, 2856, 1675, 1459, 1235, 1068 cm^{-1}; LRMS *m/z* calcd for $C_{19}H_{35}O$ $(MH)^+$ 279.2, found 279.2.

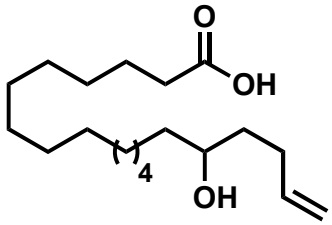


4-benzyl-2-(but-3-enyl)-1-oxa-4-azacyclohexadecan-16-one (2.30). Prepared according to the general procedure as described for the preparation of **2.18** using 16-(benzyl(2-hydroxy-1-phenylhex-5-enyl)amino)hexadecanoic acid (0.035 g, 0.090 mmol), THF (3.0 mL), Et_3N (0.032 mL, 0.23 mmol), 2,4,5-trichlorobenzoyl chloride (0.019 mL, 0.12 mmol), toluene:THF (3:1, 50 mL), and a solution of DMAP (0.22 g, 1.8 mmol) in toluene (100 mL) to give 15 mg of macrolactone **2.30** (43%) as a clear yellow oil. R*f* 0.65 (10:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5 H), 5.76 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1H), 5.17-5.13 (m, 1H), 5.00-4.92 (m, 2H), 3.85 (d, *J* = 13.6 Hz, 1H), 3.24 (d, *J* = 13.7 Hz, 1H), 2.68 (dd, *J* = 13.7, 8.8 Hz, 1 H), 2.64 (ddd, *J* = 12.7, 7.3, 7.3 Hz, 1 H), 2.38-2.26 (m, 4H), 2.02-1.98 (m, 2H), 1.85-1.76 (m, 1H), 1.64-1.25 (m,

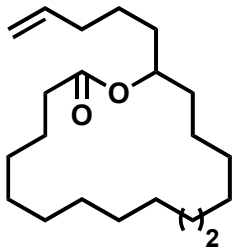
19H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 140.0, 138.1, 129.2, 128.2, 127.0, 115.0, 71.2, 59.1, 57.8, 54.4, 34.3, 32.2, 29.8, 27.3, 27.1, 27.0, 26.4, 26.2, 26.0, 26.0, 25.4, 24.0; IR (neat) 2927, 2856, 1731, 1453, 1071 cm^{-1}; LRMS *m/z* calcd for $C_{25}H_{40}NO_2$ $(MH)^+$ 386.2, found 386.1.



3-benzyl-19-oxa-3-azabicyclo[13.3.1]nonadec-15-ene (2.32). Prepared according to the general procedure as described above for the preparation of **6** using $TiCl_4$ (0.091 mL, 0.83 mmol) in CH_2Cl_2 (3.8 mL), THF (0.438 mL, 5.00 mmol), TMEDA (0.755 mL, 5.00 mmol, activated Zn dust (0.122 g, 1.87 mmol), $PbCl_2$ (0.028 g, 0.099 mmol), and a solution of macrolactone **2.19** (0.010 g, 0.026 mmol) and CH_3CHBr_2 (0.075 mL, 0.83 mmol) in CH_2Cl_2 (0.35 mL + 0.35 mL rinse) to give 6.4 mg of cyclic enol ether **2.32** (69 %) as a clear yellow oil. R*f* 0.40 (20:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.38 (d, *J* = 7.4 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.1 Hz, 1H), 4.45 (broad s, 1H), 3.89 (broad s, 1H), 3.68 (d, *J* = 14.1 Hz, 1H), 3.50 (d, *J* = 13.7 Hz, 1H), 2.71 (dd, *J* = 13.2, 7.3 Hz, 1H), 2.62-2.58 (m, 1H), 2.53-2.51 (m, 1 H), 2.40 (broad dd, *J* = 13.7, 3.0 Hz, 1 H), 2.09-1.89 (m, 4H), 1.68-1.26 (m, 20H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 154.9, 141.1, 129.3, 128.9, 128.5, 127.1, 95.7, 74.8, 59.9, 58.9, 54.9, 35.0, 30.3, 27.5, 27.4, 27.1, 26.9, 26.4, 26.3, 26.0, 26.0, 21.1; IR (neat) 2925, 2854, 1676, 1455, 1071 cm^{-1}; LRMS *m/z* calcd for $C_{24}H_{38}NO$ $(MH)^+$ 356.3, found 356.1.

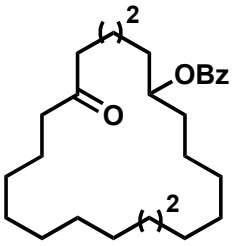


15-hydroxyicos-19-enoic acid (2.24). Prepared according the general procedure described above for the preparation of **2.21** using 16-hydroxyhexadecanoic acid (0.125 g, 0.460 mmol), DMSO (1.0 mL), IBX (0.14 g, 0.51 mmol), and pentenyl magnesium bromide (12 mL of a 0.83 M solution in THF, 10 mmol) to give 110 mg of *seco*-acid **2.24** (70%) as a white, waxy solid. mp 63-65 °C; R*f* = 0.45 (1:1 EtOAc/hexanes); 500 MHz ^{1}H NMR (CDCl3) δ 5.80 (dddd, *J* = 17.0, 10.2, 6.6, 6.6 Hz, 1H), 5.02 (dddd, *J* = 17.2, 2.0, 1.6, 1.6 Hz, 1H), 4.96 (dddd, *J* = 10.2, 2.2, 1.2, 1.2 Hz, 1 H), 3.63-3.59 (m, 2H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.12-2.05 (m, 2H), 1.64 (pentuplet, *J* = 7.4 Hz, 2 H), 1.60-1.26 (m, 27 H); ^{13}C NMR (CDCl3) δ 178.9, 139.0, 114.8, 72.2, 37.7, 37.1, 34.1, 34.0, 29.9, 29.8, 29.8, 29.7, 29.6, 29.4, 29.2, 25.8, 25.1, 24.9; IR (neat) 3210 (broad), 2914, 2847, 1695, 912 cm^{-1}; LRMS Calcd for $C_{21}H_{41}O_3$ *m/z* $(M+H)^+$ 340.3, found: 341.4



17-(pent-4-enyl)oxacycloheptadecan-2-one, 2.25. Prepared according to the general procedure as described for the preparation of **2.18** using 16-hydroxyhenicos-20-enoic acid (0.037 g, 0.11 mmol), THF (3.8 mL), Et_3N (0.14 mL 0.28 mmol), 2,4,5-trichlorobenzoyl chloride (0.022 mL, 1.4 mmol), a 3:1 mixture of toluene and THF (50 mL), and a solution of DMAP (0.262 g, 2.16 mmol) in toluene (70 mL) to give 32 mg of

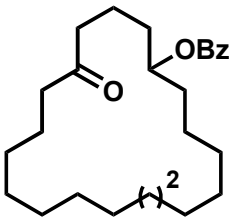
macrolactone **2.25** (92%) as a clear colorless oil. R*f* 0.25 (50:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84-5.74 (m, 1H), 5.00 (partially obscured d, *J* = 17.1 Hz, 1 H), 4.98-4.92 (m, 2H), 2.38-2.26 (m, 2H), 2.06 (q, *J* = 6.7 Hz, 2H), 1.76-1.67 (m, 1 H), 1.62-1.27 (m, 29 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 138.7, 114.9, 74.2, 34.9, 34.6, 34.3, 33.8, 29.9, 28.6, 28.5, 28.4, 28.0, 27.8, 27.2, 27.1, 26.9, 25.2, 24.9, 24.9; IR (neat) 2927, 2856, 1733, 1459, 1260, 1099 cm^{-1}; LRMS calcd *m/z* for $C_{21}H_{39}O_2$ $(MH)^+$ 323.3, found: 323.4



21-oxabicyclo[14.4.1]henicos-1(20)-ene, 2.33. Prepared according to the general procedure as described above for the preparation of **2.19** using $TiCl_4$ (0.091 mL, 0.83 mmol) in CH_2Cl_2 (8.8 mL), THF (1.04 mL, 11.9 mmol), TMEDA (1.8 mL, 12 mmol) activated Zn dust (0.290 g, 4.46 mmol), $PbCl_2$ (0.065 g, 0.24 mmol), and a solution of macrolactone **2.25** (0.020 g, 0.062 mmol) and CH_3CHBr_2 (0.177 mL, 1.98 mmol) in CH_2Cl_2 (0.85 mL + 0.85 mL rinse) to give 20 mg of cyclic enol ether **2.33** (87 %) as a clear yellow oil R*f* 0.71 (50:1 hexanes/EtOAc). Because of its instability, enol ether **2.33** was characterized as the corresponding ketobenzoate as described below.

To a solution of enol ether **2.33** (0.095 mmol) in CH_2Cl_2 (9.5 mL) at rt was added silica gel (ca. 0.500 g). The resulting slurry was stirred for 8 h and then filtered using EtOAc (50 mL). The filtrate was concentrated and the resulting yellow residue that contained 6-hydroxycycloicosanone was immediately converted into the corresponding benzoyl ester as described below.

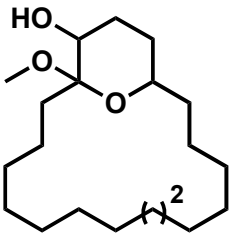
To a solution of hydroxy ketone (0.095 mmol) in CH_2Cl_2 (4.75 mL) at rt was added Et_3N (0.040 mL, 0.28 mmol) and benzoyl chloride (0.028 mL, 0.24 mmol). The reaction mixture was allowed to stir for 4 h and was then diluted with Et_2O (50 mL) and the reaction was quenched with sat. $NaHCO_3$ (aq., 15 mL). The organic phase was washed with sat. $NaHCO_3$ (aq., 4 x 15 mL), H_2O (25 mL), brine (25 mL), dried ($MgSO_4$), and concentrated. Preparative TLC (10:1 hexanes/EtOAc) gave 17 mg of benzoate (42% from **2.25**) as a colorless oil. R*f* 0.43 (10:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.3 Hz, 2 H), 7.56 (t, *J* = 7.1 Hz, 1 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 5.08 (ddd, *J* = 12.2, 6.1, 6.1, 6.1 Hz, 1H), 2.41 (partially obscured t, *J* = 7.1 Hz, 2 H), 2.38 (partially obscured t, *J* = 7.1 Hz, 2 H), 1.70-1.57 (m, 8H), 1.31 (m, 24H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 166.5, 133.2, 131.6, 130.6, 129.9, 128.8, 74.9, 42.9, 42.6, 33.5, 33.1, 28.8, 28.7, 28.6, 28.5, 28.4, 28.4, 28.3, 28.3, 28.2, 24.9, 24.7 24.3, 24.1; IR (neat) 2927, 2855, 1714, 1451, 1274, 1113 cm^{-1}; LRMS *m/z* calcd for $C_{27}H_{43}O_3$ $(MH)^+$ 415.3, found 415.4.



5-oxocyclononadecyl benzoate (2.34). To a solution of enol ether **2.31** (0.087 mmol) in CH_2Cl_2 (8.7 mL) at rt was added silica gel (ca. 0.500 g). The resulting slurry was stirred for 5 h and then filtered using EtOAc (50 mL). The filtrate was concentrated and the resulting yellow residue that contained 5-hydroxycyclononadecanone was immediately converted into the corresponding benzoyl ester as described below.

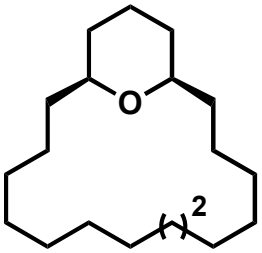
To a solution of the 5-hydroxycyclononadecanone (0.087 mmol) from above in

CH_2Cl_2 (4.4 mL) at rt was sequentially added Et_3N (0.20 mL, 0.26 mmol) and benzoyl chloride (0.18 mL, 0.22 mmol). After stirring for 4 h the reaction mixture was diluted with ether (50 mL) and the reaction was quenched with sat. $NaHCO_3$ (aq., 15 mL). The organic phase was washed with sat. $NaHCO_3$ (aq., 4 x 15 mL), H_2O (25 mL), brine (25 mL), dried ($MgSO_4$), and concentrated. Preparative TLC (10:1 hexanes/EtOAc) gave 3.0 mg of benzoyl ketone **2.34** (63% from **2.23**) as a colorless, viscous oil. R*f* 0.30 (10:1 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-8.04 (m, 2H), 7.58-7.55 (m, 1H), 7.46-7.43 (m, 2H), 5.12 (ddd, *J* = 11.8, 6.0, 6.0 Hz, 1H), 2.52 (ddd, *J* = 16.1, 6.8, 6.8 Hz, 1 H), 2.48-2.36 (m, 3H), 1.80-1.58 (m, 8H), 1.40-1.32 (m, 22H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 133.0, 130.9, 129.8, 128.5, 74.2, 42.7, 42.3, 33.4, 32.9, 28.6, 28.4, 28.2, 28.1, 28.1, 28.0, 27.9, 27.9, 27.7, 24.1, 23.9, 19.8; IR (neat) 2927, 2855, 1714, 1453, 1274, 1113 cm^{-1}; LRMS *m/z* calcd for $C_{26}H_{41}O_3$ $(MH)^+$ 401.2, found: 401.1

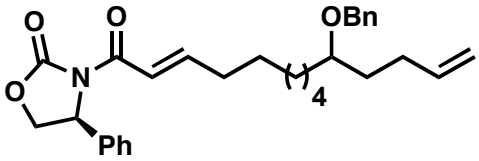


16-methoxy-20-oxabicyclo[14.3.1]icosan-17-ol, 2.35. To a solution of enol ether **2.31** (0.043 mmol) in MeOH (1.00 mL) at 0 °C was added meta-chloroperoxybenzoic acid (77%) (11.0 mg, 0.047 mmol). After stirring at 0 °C for 3 h, the reaction was quenched with sat. $Na_2S_2O_3$ (aq., 10 mL), and the resulting mixture diluted with ether (20 mL). The organic phase was washed with $NaHCO_3$ (aq., 2 x 10 mL) and sat. NaCl (aq., 10 mL). The organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography (hexanes:ethyl acetate, 20:1) gave 9.5 mg of hydroxy ketal **2.35** (68%) as a 3:1 mixture of diastereomers as a clear colorless oil: R*f* 0.35 (10:1 hexanes/EtOAc); $_1$H NMR (500

MHz, $CDCl_3$) δ 3.63-3.59 (m, 1H), 3.52-3.50 (m, 1H), 3.27 (s, 3H, major diastereomer), 3.23 (s, 3H, minor diastereomer), 2.07 (dddd, J = 13.7, 13.7, 4.9, 2.4 Hz, 1H), 1.81-1.26 (m, 31H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.3, 69.8, 69.1, 47.4, 35.2, 32.1, 30.7, 28.6, 28.4, 28.1, 28.1, 27.8, 27.7, 27.6, 27.4, 27.3, 27.2, 24.1, 22.8; LRMS Calcd for $C_{19}H_{37}O$ *m/z* $(MNa)^+$ 349.2, found 349.2.

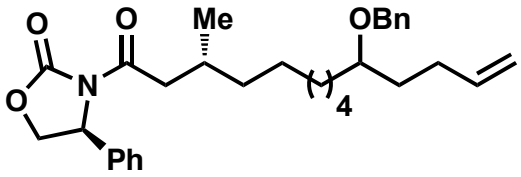


20-oxabicyclo[14.3.1]icosane, 2.36. To a solution of enol ether **2.31** (0.025 g, 0.089 mmol) and triethylsilane (0.043 mL, 0.267 mmol) in CH_2Cl_2 (1.00 mL) at 0 °C was added trifluoroacetic acid (0.013 mL, 0.18 mmol). After 10 min, the reaction was quenched with sat. $NaHCO_3$ (aq., 10 mL), and the resulting mixture diluted with ether (20 mL). The organic phase was washed with H_2O (10 mL) and sat. NaCl (aq., 10 mL). The organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography (hexanes to hexanes:ethylacetate, 100:1)gave 21 mg of tetrahydropyran **2.36** (87%)asaclearcolorless oil: R*f* 0.42 (50:1 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 3.2 (t, J = 9.8 Hz, 2H), 1.79-1.16 (m, 34 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.9, 32.6, 28.9, 28.5, 27.7, 27.6, 27.5, 25.6, 24.3; IR (neat) 2927, 2855, 1457, 1085 cm^{-1}; LRMS Calcd for $C_{19}H_{37}O$ *m/z* $(MH)^+$ 281.2, found 281.1.



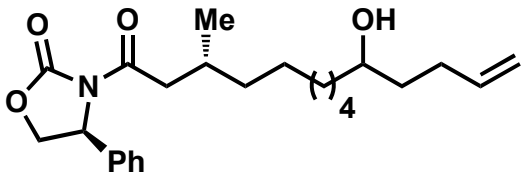
(*S*, *E*)-3-(11-(benzyloxy)pentadeca-2,14-dienoyl)-4-phenyloxazolidin-2-one, (2.44). To

a solution of (*S*)-phosphonate **2.43** (0.609 g, 1.79 mmol) in THF (4.5 mL) at 0 °C was added sodium hexamethyldisilazide (1.50 mL of a 1.0 M solution in THF, 1.50 mmol). After 5 min, the cooling bath was removed and the reaction mixture was warmed to rt. After 1 h the solution was cooled to 0 °C and a solution of aldehyde **2.42** (0.377 g, 1.19 mmol) in THF (3.30 mL) was added. After 2 h, the reaction was quenched with pH 7 phosphate buffer (10 mL) and the resulting mixture diluted with EtOAc (50 mL). The organic phase was washed with 1M $KHSO_4$ (aq., 20 mL), H_2O (20 mL), sat. $NaHCO_3$ (aq., 20 mL), and sat. NaCl (aq., 20 mL). The organic layer was dried (Na_2SO_4) and concentrated. Flash chromatography (hexanes:ethyl acetate, 10:1 to 5:1) gave 417 mg of unsaturated imide **2.44** (70%) as a clear colorless oil: R*f* 0.62 (5:3 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.16 (m, 10H), 7.04-6.98 (m, 1H), 5.74 (dddd, *J* = 17.1, 10.25, 6.8, 6.8 Hz, 1H), 5.38 (dd, *J* = 8.79, 3.9 Hz, 1H), 4.93 (ddd, *J* = 17.1, 2.0, 2.0 Hz, 1H), 4.80 (dd, *J* = 10.3, 1.0 Hz, 1H), 4.58 (t, *J* = 8.8 Hz, 1H), 4.41 (dd, *J* = 16.1, 11.2 Hz, 2H), 4.17 (ddd, *J* = 8.8, 1.5, 3.9, Hz, 1H), 3.31 (dddd, *J* = 11.7, 5.9, 5.9, 5.9 Hz, 1H), 2.17 (ddd, *J* = 7.3, 7.3, 7.3 Hz, 2H), 2.12-2.01 (m, 2H), 1.61-1.19 (m, 19H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 153.8, 152.4, 139.3, 139.2, 138.9, 129.3, 129.3, 128.7, 128.5, 128.4, 128.4, 128.4, 128.4, 127.9, 127.5, 127.5, 126.1, 120.3, 114.6, 78.5, 77.5, 77.2, 77.0, 57.9 (2), 33.9 (2), 33.3 (2), 32.9 (2), 29.9 (2), 29.8 (3), 29.6 (3), 29.5 (2), 29.3 (3), 28.2 (3), 25.4; DEPT (125 MHz, $CDCl_3$) δ CH_2: 114.6, 70.9, 70.1, 33.9, 33.3, 32.9, 29.9, 29.8, 29.6, 29.5, 29.3, 28.2, 25.4. CH: 152.4, 138.9, 129.3, 128.7, 128.4, 127.9, 127.5, 126.1, 120.3, 78.5, 57.9; IR (neat) 2929, 2855, 1781, 1689, 1636, 1455, 1383, 1350, 1200, 1066 cm^{-1}; LRMS *m/z* calcd for $C_{33}H_{45}NO_4$ $(MH)^+$ 503.3, found 504.1.

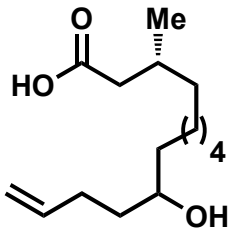


(*S*)-3-((*R*)-11-(benzyloxy)-3-methylpentadec-14-enoyl)-4-phenyloxazolidin-2-one, (2.45). To a slurry consisting of CuBr•SMe_2 (0.421 g, 2.05 mmol) and THF (3.5 mL) was added Me_2S (2.35 mL) and cooled to -78 °C. To this was slowly added MeMgBr (0.95 mL of a 3.0 M solution in Et_2O, 1.10 mmol). After 20 min, the mixture was warmed to 0° C and kept at that temperature for 0.5 h. The reaction mixture was cooled to -78 °C and transferred to a solution of enimide **2.44** (413 mg, 0.821 mmol) in THF (2.0 mL) and CH_2Cl_2 (1.0 mL) at -78 °C. After 0.5 h, the reaction mixture was warmed to -40 °C and allowed to stir for 2.5 h after which the reaction was quenched with pH 7 phosphate buffer (20 mL) and diluted with 1:1 EtOAc:hexanes (50 mL). The organic phase was washed with 1 M $KHSO_4$ (aq., 2 x 25 mL), H_2O (25 mL), and sat. NaCl (aq., 25 mL). The organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (hexanes:ethyl acetate, 50:1 to 20:1 to 10:1) gave 282 mg of enimide **2.44** (69%) as a clear colorless oil: R*f* 0.74 (5:3 hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.27 (m, 10 H), 5.84 (dddd, *J* = 16.6, 9.8, 6.4, 6.4 Hz, 1H), 5.44 (dd, *J* = 8.8, 3.9 Hz, 1H), 5.03 (ddd, *J* = 16.4, 1.5, 1.5 Hz, 1H), 4.97-4.95 (m, 1H), 4.68 (dd, *J* = 9.3, 9.3 Hz, 1H), 4.26 (dd, *J* = 8.8, 3.4 Hz, 1 H), 3.41 (ddd, *J* = 5.8, 5.8, 5.8 Hz, 1 H), 2.85 (d, *J* = 6.8 Hz, 2 H), 2.23-2.09 (m, 2 H), 2.03-1.95 (m, 1 H), 1.70-1.47 (m, 4 H), 1.40-1.20 (m, 13 H), 0.80 (d, *J* = 6.83 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 153.9, 139.4, 139.3, 139.0, 129.3, 128.8, 128.5, 127.9, 127.6, 126.1, 114.6, 78.6, 77.5, 77.2, 77.0, 71.0, 70.0, 57.8, 42.8, 36.8, 34.0, 33.3, 30.0, 29.9, 29.9, 29.8, 29.8, 27.1, 25.5, 19.9; DEPT (125 MHz, $CDCl_3$) δ CH_3: 19.9. CH2: 114.6, 71.0, 70.0, 42.8, 36.8, 34.0, 33.4, 30.0, 29.9,

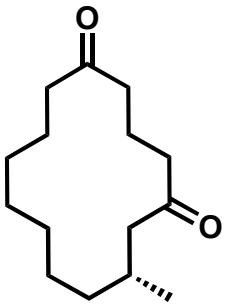
29.8, 27.2, 25.5, 19.9. CH: 139.0, 129.3, 128.8, 128.5, 128.0, 127.6, 126.1, 78.6, 57.8, 29.9. IR (neat) 2928, 2855, 1783, 1706, 1384, 1324, 1200, 1064 cm^{-1}; LRMS *m/z* calcd for $C_{33}H_{45}NO_4Na$ $(M+Na)^+$ 542.3, found 542.4.



(*S*)-3-((*R*)-11-hydroxy-3-methylpentadec-14-enoyl)-4-phenyloxazolidin-2-one, (S1). To a mixture of imide **2.45** (0.282 g, 0.558 mmol), CH_2Cl_2 (9.0 mL), and H_2O (1.0 mL) at 0 ºC was added DDQ (0.252 g, 1.11 mmol). After 4 h the reaction was quenched with sat. $NaHCO_3$ (aq., 30 mL) and diluted with CH_2Cl_2 (40 mL). The organic phase was washed with sat. $NaHCO_3$ (aq., 30 mL) and sat. NaCl (aq., 20 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes:EtOAc, 10:1 to 5:1) gave 0.213 g of imide **S1** (92%) as a clear colorless oil: R*f* 0.60 (5:3 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.36-7.23 (m, 5H), 5.82 (dddd, *J* = 17.1, 13.4, 6.8, 3.4 Hz, 1H), 5.41 (ddd, *J* = 8.7, 3.6, 3.6 Hz, 1H), 5.02 (dddd, *J* = 17.1, 3.4, 3.4, 2.0 Hz, 1H), 4.94 (dddd, *J* = 10.2, 3.4, 3.4, 1.5 Hz, 1H), 4.64 (ddd, *J* = 8.8, 8.8, 3.4 Hz, 1H), 4.23 (ddd, *J* = 8.7, 4.0, 4.0 Hz, 2H), 3.61-3.55 (broad m, 1H), 2.80 (dd, *J* = 6.8, 3.4 Hz, 2H), 2.22-2.06 (m, 2H), 1.98-1.92 (m, 2H), 1.70 (brs, 1H), 1.58-1.18 (m, 16H), 0.84 (d, *J* = 6.4, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 153.9, 139.4, 138.9, 129.3, 128.8, 126.1, 114.9, 71.7, 70.0, 57.8, 42.8, 37.7, 36.7, 36.7, 30.3, 29.9, 29.9, 29.8, 29.7, 29.7, 29.7, 27.1, 25.8, 19.9; IR (neat) 3500, 2927, 2854, 2784, 1705, 1385, 1325, 1200 cm^{-1}; LRMS *m/z* calcd for $C_{26}H_{40}NO_4$ $(MH)^+$ 430.3, found 430.1.



(*R*)-11-hydroxy-3-methylpentadec-14-enoic acid, (2.46). To a mixture of imide **S1** (0.213 g, 0.513 mmol), THF (4 mL), and H_2O (1.1 mL) at 0 ºC was added H_2O_2 (0.20 mL of a 50% aq. solution) dropwise followed by LiOH (0.025 g, 1.0 mmol). The reaction mixture was kept at 0 °C for 5 min and then warmed to rt and kept at that temperature for 2 h. The reaction was quenched with sat. Na_2SO_3 (aq., 5 mL), stirred for 10 min, and then concentrated to remove THF. The resulting aqueous residue was acidified to pH 3 (glacial acetic acid) and exacted with EtOAc (3 x 100 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes:EtOAc, 5:3) gave 113 mg of *seco*-acid **2.46** (77%) as a clear colorless oil: R*f* 0.20 (5:3 hexanes/EtOAc); $[\alpha]_D^{20}$ +2.66 (*c* = 1.135, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dddd, *J* = 17.1, 10.3, 6.8, 6.8 Hz, 1H), 5.06 (ddd, *J* = 17.1, 3.4, 1.4 Hz, 1H), 4.99-4.96 (m, 1H), 3.66-3.62 (m, 1H), 2.34 (ddd, *J* = 15.1, 6.3, 1.9 Hz, 1H), 2.25-2.10 (m, 3H), 1.99-1.92 (m, 1H), 1.61-1.21 (m, 18H), 0.97 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 114.9, 71.9, 71.8, 37.6, 36.8, 36.7, 36.6, 36.6, 30.4, 30.3, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 27.0, 25.7, 19.9; DEPT (125 MHz, $CDCl_3$) δ CH_3 19.9; CH_2 114.9, 37.6, 36.8, 36.7, 36.6 (2), 30.2, 29.8, 29.7, 29.6, 29.6, 29.6, 29.5, 27.0, 25.7; CH: 138.8, 71.8 (2), 30.4. IR (neat) 3500-2700 (broad), 2928, 2855, 1710, 1489, 1294 cm^{-1}; LRMS *m/z* calcd for $C_{17}H_{32}O_3$ $(M+Na)^+$ 307.2, found 307.1.



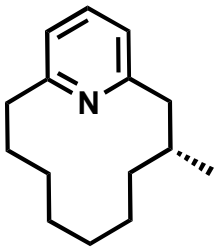
(*R*)-7-methylcyclopentadecane-1,5-dione. To a solution of *seco*-acid **2.46** (20. mg, 0.074 mmol) in THF (4.8 mL) at rt was added Et_3N (0.053 mL, 0.37 mmol) and 2,4,5-trichlorobenzoyl chloride (0.030 mL, 0.19 mmol). After 5 h the reaction mixture was diluted with a 3:1 mixture of toluene and THF (50 mL) and then transferred over 14 h into a solution of DMAP (351 mg, 2.88 mmol) in toluene (120 mL) at 48 ºC. The reaction mixture was stirred for an additional 2 h and then concentrated. The resulting residue was passed through a plug of silica gel and then concentrated to give 16 mg of macrolactone **2.47** (81%) as a clear colorless oil: R*f* 0.40 (10:1 hexanes/EtOAc). Macrolactone **2.47** was taken on directly to the olefinic-lactone cyclization reaction to give **2.48** as described below.

Macrocyclic enol ether **2.48** was prepared according to the general procedure as described for the preparation of **2.19** using $TiCl_4$ (0.21 mL, 1.9 mmol) in CH_2Cl_2 (8.6 mL), THF (1.0 mL, 12 mmol), TMEDA (1.7 mL, 12 mmol), activated Zn dust (0.28 g, 4.3 mmol), $PbCl_2$ (0.063 g, 0.23 mmol), and a solution of macrolactone **2.47** (0.016 g, 0.060 mmol) and CH_3CHBr_2 (0.17 mL, 1.9 mmol) in CH_2Cl_2 (1.0 mL + 1.0 mL rinse) to give 12.1 mg of cyclic enol ether **2.48** (69 %) as a clear yellow oil. **2.48** was taken directly to the hydrolysis step to give **2.49** as described below.

To a solution of enol ether **2.48** in CH_2Cl_2 (8.7 mL) at rt was added silica gel (ca. 0.5 g). The resulting slurry was stirred at room temperature for 6 h. The reaction mixture was

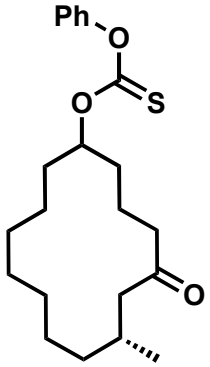
concentrated and filtered using EtOAc (50 mL). The filtrate was concentrated to afford 12.6 mg of **2.49** (98%) as a yellow residue that was immediately taken to the subsequent diketone or thiocarbonate formation.

To a solution of hydroxy ketone **2.49** (0.050 mmol) from above in CH_2Cl_2 (1.00 mL) at 0 °C was added the Dess-Martin periodinane (0.042 g, 0.10 mmol). The reaction was allowed to stir for 1 h and then loaded directly onto a silica gel column (hexanes:ethyl acetate, 50:1 to 20:1 to 10:1) to give 11.2 mg of diketone **2.50** (89% from **2.46**) as a crystalline solid. R*f* 0.22 (10:1 hexanes/EtOAc); $[\alpha]_D^{20}$ -5.33 (*c* = 0.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.67-2.27 (m, 7H), 2.15 (dd, *J* = 15.4, 4.0 Hz, 1H), 2.11-2.03 (m, 1H), 1.89-1.82 (m, 2H), 1.78-1.68 (m, 1H), 1.62-1.52 (m, 1H), 1.34-1.08 (m, 12H), 0.93 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1, 211.4, 50.3, 41.8, 41.5, 41.4, 36.5, 29.1, 28.1, 27.5, 27.4, 26.9, 25.4, 23.5, 21.9, 17.6; IR (neat) 2927, 2853, 1706, 1400, 1065 cm^{-1}; LRMS *m/z* calcd for $C_{16}H_{28}O_2Na$ $(M+Na)^+$ 275.2, found 275.2.



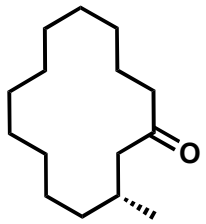
(*R*)-(+)-Muscopyridine. A solution of diketone **2.50** (0.016 g, 0.063 mmol), EtOH (3.2 mL) and hydroxylamine hydrochloride (0.11 g, 1.6 mmol) was heated at 160 °C for 18.5 h in a sealed tube. After the reaction mixture was cooled to rt, it was diluted with ether (7 mL) and the reaction was quenched with $NaHCO_3$ (ca. 0.15 g). The resulting mixture was filtered through SiO_2 using EtOAc. Concentration and flash chromatography (50:1 to 20:1 hexanes:ethyl acetate) gave 5.7 mg of muscopyridine (41%) as a colorless oil: R*f*

0.78 (5:1 hexanes/EtOAc); $[\alpha]_D^{20}$ +7.3 (*c* = 0.58, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) d 7.48 (t, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 6.6 Hz, 2H), 2.94 (dd, *J* = 13.2, 3.7 Hz, 1H), 2.91-2.78 (partially obscured m, 1H), 2.52 (dd, *J* = 12.8, 10.0 Hz, 1 H), 2.10-2.00 (m, 1H), 1.82 (pentuplet, *J* = 6.1 Hz, 2H), 1.27-1.15 (m, 13H), 1.07 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 161.3, 136.7, 121.1, 120.8, 45.8, 37.4, 34.6, 34.1, 30.2, 28.3, 26.9, 26.7, 26.5, 25.6, 23.5, 22.6; IR (neat) 2926, 2854, 1576, 1458 cm^{-1}; LRMS *m/z* calcd for $C_{16}H_{26}N(MH)^+$ 232.2, found 232.3.

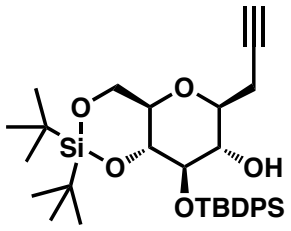


***O*-(7*R*)-7-methyl-5-oxocyclopentadecyl *O*-phenyl carbonothioate S2.** To a solution of hydroxy ketone **2.49** (0.058 mmol) in CH_2Cl_2 (0.75 mL) at 0 °C was added pyridine (0.10 mL, 0.90 mmol), DMAP (ca. 0.010 g) and phenyl chlorothionoformate (0.040 mL, 0.29 mmol). The reaction was allowed to slowly warm to rt over 10 h before being quenched with sat. NH_4Cl (aq., 10 mL) and diluted with a 1:1 mixture of EtOAc/hexanes (50 mL). The organic phase was washed with H_2O (10 mL), and sat. NaCl (aq., 10 mL), dried (Na_2SO_4), and concentrated. Flash chromatography (hexanes:ethyl acetate, 50:1 to 20:1 to 10:1) gave 7.5 mg of thiocarbonate **S2** (33%) as a clear colorless oil: R*f* 0.74 (5:3 hexanes/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (dt, *J* = 7.5, 1.3 Hz, 2H), 7.31 (partially obscured dt, *J* = 7.0, 1.1 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 2H), 5.34 (dddd, *J* = 5.5, 5.5, 5.5, 5.5 Hz, 1H), 2.69-2.61 (m, 1H), 2.51-2.40 (m, 2H), 2.22 (dd, *J* = 15.3, 4.2 Hz,

1H), 2.12-2.03 (m, 1H), 1.90-1.80 (m, 4H), 1.74-1.64 (m, 2H), 1.44-1.20 (m, 14H), 0.96 (d, J = 6.8, 1.5 H), 0.95 (d, J = 6.8 Hz, 1.5 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 195.0, 153.6, 129.7, 126.7, 122.2, 84.5, 50.7, 42.1, 36.2, 31.7, 31.7, 29.3, 27.4, 26.9, 26.7, 26.5, 25.6, 23.5, 21.6, 19.3; IR (neat) 2927, 2857, 1710, 1490. 1457. 1276, 1200 cm^{-1}; LRMS m/z calcd for $C_{23}H_{34}O_3SNa$ $(M+Na)^+$ 413.2, found 413.2.

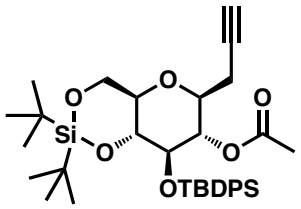


(*R*)-(-)-Muscone. To a solution of thiocarbonate **S2** (0.075 g, 0.019 mmol) and Bu_3SnH (0.022 mL, 0.022 mmol) in toluene (3.5 mL) was added a spatula tip of AIBN. The reaction mixture was then heated at reflux for 4 h, cooled to rt, and loaded directly onto a silica gel column (hexanes:ethyl acetate, 50:1 to 20:1) to give 4.5 mg of muscone (97%) as a colorless oil. Rf 0.74 (5:3 hexanes/EtOAc); $[\alpha]_D^{20}$ -7.3 (c = 0.54, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.46-2.40 (m, 3H), 2.18 (dd, J = 15.2, 5.1 Hz, 1H), 2.12-2.02 (m, 1H), 1.73-1.55 (m, 2H), 1.40-1.20 (brs, 20H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.3, 50.6, 49.3, 35.8, 29.9, 29.3, 27.8, 27.3, 26.9, 26.8, 26.8, 26.7, 26.5, 26.4, 25.2, 23.3, 21.3; IR (neat) 2924, 2853, 1710, 1460, 1109 cm^{-1}; LRMS Calcd for $C_{16}H_{31}O$ m/z $(MH)^+$ 239.2, found 239.2.

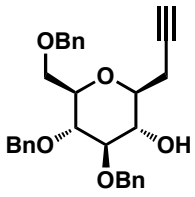


Propargyl 3-*O*-TBDPS-4,5-bis-*t*-butyl-dioxasiline-D-glucopyranoside, 2.66.

To a solution of the D-glucopyranoside **2.64** (350 mg, 0.687 mmol, 1.00 eq) in CH_2Cl_2 (3.40 mL, 0.2 M) at 0 °C was added dimethyldioxirane (17.2 mL of a 0.1 M solution, 1.72 mmol, 2.50 eq). After stirring for 10 minutes, the reaction was concentrated under high vacuum to afford the corresponding epoxide. The resulting clear oil was taken up in THF (5.73 mL, 0.12 M) and cooled to 0 °C. To this solution was added propargyl magnesium bromide (1.43 mL of a 1.20 M solution in ether, 1.72 mmol, 2.50 eq); prepared from the addition of neat propargyl bromide (1.52 mL, 0.15 mmol, 1.00 eq) to a slurry of magnesium turnings (365 mg, 0.15 mmol, 1.00 eq) and a catalytic amount of $HgCl_2$ (ca. 0.001 g) in ether (11.50 ml, 1.20 M). After stirring for 20 minutes at 0 °C, the reaction was allowed to warm to RT over 1 h and then quenched with sat. aq. NH_4Cl. After stirring for 10 min, the mixture the aqueous phase was separated and was extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (Hexanes-EtOAc 50:1, then 20:1) afforded alcohol **2.66** (287 mg, 72%) as a colorless oil. ^{1}H NMR (500 MHz, C_6D_6): d 7.95-7.93 (m, 2H), 7.82-7.80 (m, 2H), 7.28-7.21 (m, 6H), 4.13-4.10 (dd, *J* = 9.7, 4.8 Hz, 1H), 3.98 (t, *J* = 9.28, 9.28 Hz, 1H), 3.96 (t, *J* = 10.26, 10.26 Hz, 1H), 3.73 (t, *J* = 8.79, 8.79 Hz, 1H), 3.15 (ddd, *J* = 10.26, 10.26, 5.24 Hz, 1H), 2.89 (ddd, *J* = 9.28, 5.86, 3.42 Hz, 1H), 2.46-2.28 (m, 2H), 1.74 (t, *J* = 2.4, 2.4 Hz, 1H), 1.21 (s, 9H), 1.09 (s, 9H), 1.04 (s,9H); ^{3}C (125MHz, C_6D_6): 137.2, 136.1, 135.7, 133.1, 130.6, 130.4, 81.4, 80.9, 78.6, 77.6, 75.4, 74.7, 70.7,67.1, 28.1 27.6, 23.2, 22.4, 20.5. IR(CH_2Cl_2) 2891, 2859, 1744, 1483, 1225, 1106 cm^{-1}. LRMS calc'd for $C_{30}H_{32}O_5$ (MH^+) 580.3, found 580.3.

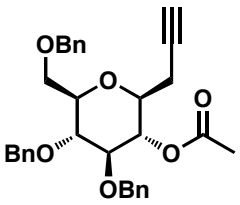


2,2-di-*tert*-butyl-8-(*tert*-butyldiphenylsilyloxy)-6-(propynyl)hexahydropyrano[3,2-*d*][1,3,2]dioxasilin-7-yl acetate, 2.67 To a solution of alcohol **2.66** (100 mg, 0.172 mmol) and CH_2Cl_2 (0.81 mL, 0.20 M) at RT was sequentially added $(i\text{-Pr})_2NEt$ (0.238 mL, 1.37 mmol, 8.0 eq), acetic anhydride (0.097 mL, 1.03 mmol, 6.0 eq) and DMAP (ca. 0.005 g). After stirring overnight, the reaction was quenched with sat. aq. NH_4Cl (50 mL). The layere were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL), dried over Na_2SO_4 and concentrated. Flash chromatography (Hexanes-EtOAc 50:1, then 20:1) gave acetate **2.67** (98.2 mg, 98%) as a clear viscous oil. ^1H NMR (500 MHz, C_6D_6): d 8.08-8.00 (m, 2H), 7.74-7.70 (m, 2H), 7.35-7.26 (m, 6H), 4.98 (t, J = 9.28, 9.28 Hz, 1H), 4.08 (dd, J = 10.25, 4.88 Hz), 3.90-3.77 (m, 4H), 3.10 (ddd, J = 9.77, 9.77, 4.89 Hz, 1H), 2.90 (ddd, J = 11.72, 6.35, 4.88 Hz, 1H), 2.36-2.33 (m, 2H), 1.66 (t, J = 2.44, 2.44, 1H), 1.19 (s, 9H), 1.10 (s, 9H), 1.08 (s, 3H), 1.06 (s, 9H). ^{13}C (125 MHz, C_6D_6) d 170.73, 137.38, 136.46, 135. 46, 132.54, 130.69, 129.94, 80.87, 78.82, 78.04, 77.60, 75.5, 70.37, 66.87, 28.21, 27.66, 27.61, 23.65, 23.22, 20.68, 20.52, 20.46. LRMS calc'd for $C_{30}H_{32}O_5$ (MH^+) 623.3, found 623.3.



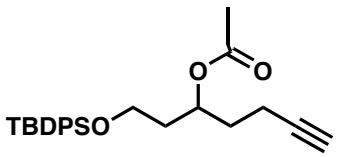
3-(3,4,6-Tri-O-benzyl-b-D-glucopyranosyl)-1-propyne, 2.69. To a solution of tri-*O*-benzyl-D-glucal **2.69** (150 mg, 0.36 mmol, 1.00 eq) in CH_2Cl_2 (1.80 mL, 0.2 M) at 0 °C

was added dimethyldioxirane (9.0 mL of a 0.1 M solution, 0.90 mmol, 2.50 eq). After stirring for 10 minutes, the reaction was concentrated under high vacuum to afford the corresponding epoxide. The resulting white solid was taken up in THF (3.0 mL, 0.12 M) and cooled to 0 °C. To this solution was added propargyl magnesium bromide (0.75 mL of a 1.20 M solution in ether, 0.90 mmol, 2.50 eq); prepared similarly as shown in the experimental details for substrate **2.66** After stirring for 20 minutes at 0 °C, the reaction was allowed to warm to RT over 1 h and then quenched with sat. aq. NH_4Cl (10 mL). After stirring for 10 min, the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (Hexanes-EtOAc 20:1, 10:1, then 5:1) afforded alcohol **2.69** (132 mg, 78%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): d 7.42-7.24 (m, 13H), 7.22-7.21 (m, 2H), 4.98 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 11.1 Hz, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 12.2 Hz, 1H), 4.62 (d, *J* = 10.8 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 3.78-3.49 (m, 6H), 3.48-3.43 (m, 1H), 2.72 (dddd, *J* = 16.7, 3.2, 3.2, 1.0 Hz, 1H), 2.58 (ddd, *J* = 17.2, 5.8, 2.7 Hz, 1H), 2.38 (s, 1H), 2.04 (dd, *J* = 2.6, 2.6 Hz, 1H); ^{13}C (125MHz, $CDCl_3$): δ 138.7, 138.4, 138.2, 128.8, 128.6, 128.5, 128.5, 128.1, 128.0, 128.0, 127.7, 86.6, 80.7, 7 9.5, 78.4, 77.8, 77.3, 77.1, 75.4, 75.0, 73.6, 73.1, 70.4, 68.9, 22.2; IR (CCl_4) 3571, 3310, 2864, 1448, 1100 cm^{-1}. LRMS calc'd for $C_{30}H_{32}O_5$ (MH^+) 473.2, found 473.2.



4,5-bis(benzyloxy)-6-(benzyloxymethyl)-2-(propynyl)tetrahydro-2*H*-pyran-3-yl-acetate, 2.70. To a solution of alcohol **2.69** (100 mg, 0.212 mmol) and CH_2Cl_2 (1.10 mL,

0.20 M) at RT was sequentially added (i-Pr)$_2$NEt (0.296 mL, 1.70 mmol, 8.00 eq), added acetic anhydride (0.120 mL, 1.27 mmol, 6.00 eq) and a catalytic amount of DMAP (ca. 0.005 g). After stirring overnight, the reaction was quenched with sat. aq. NH_4Cl (50 mL). The layers were sperated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. Flash chromatography (Hexanes-EtOAc 50:1, then 20:1) gave acetate **2.70** (104 mg, 96%) as a clear viscous oil. ^{1}H NMR (500 MHz, $CDCl_3$): d 7.33–7.15 (m, 15H), 4.99 (t, J = 9.30, 9.30 Hz), 4.85–4.52 (m, 6H), 3.80–3.62 (m, 4H), 3.53–3.42 (m, 2H), 2.49–2.45 (m, 2H), 1.99 (t, J = 2.4 Hz, 1H), 1.95 (s, 3H). ^{13}C (125 MHz, $CDCl_3$): d 138.7, 138.4, 138.2, 128.8, 128.6, 128.5, 128.5, 128.1, 128.0, 128.0, 127.7, 86.6, 80.7, 7 9.5, 78.4, 77.8, 77.3, 77.1, 75.4, 75.0, 73.6, 73.1, 70.4, 68.9, 22.2 LRMS calc'd for $C_{32}H_{34}O_6$ (MH^+) 515.2, found 515.2.

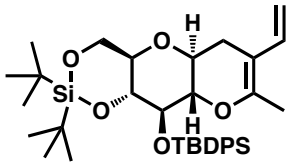


1-(*tert*-butyldiphenylsilyloxy)oct-7-yn-4-yl-acetate, 2.73. Known aldehyde **2.71**[27] (333 mg, 1.065 mmol, 1.00 eq) was taken up in THF (5.5 mL, 0.20 M) and cooled to 0°C. The TMS homopropargyl Grignard[28] (9.00 mL of a 0.26 M solution, 2.34 mmol 2.20 eq.) was added over 1 h via syringe pump. After the addition, the reaction was allowed to warm to RT and stirred overnight. The reaction was then cooled to 0°C and quenched with sat. aq. NH_4Cl (50 mL). The phases were separated and the aqueous layer was extracted with diethyl ether (3 X 50 mL). The combined organic extracts were washed with dried over Na_2SO_4 and concentrated.

The crude residue was taken up in MeOH (5.32 mL, 0.2 M) and then was added

anhyd. K_2CO_3 (gross excess) in one portion, at RT. The reaction was allowed to stir for an hour before it was diluted with H_2O (15 mL). The reaction mixture was extracted with CH_2Cl_2 (3 X 50 mL) and the combined organic extracts were dried over Na_2SO_4 and concentrated to give a yellow residue.

The crude terminal alkyne was then subjected to standard acylation conditions. (*i*-Pr)$_2$NEt (1.19 mL, 8.52 mmol, 8.00 eq), acetic anhydride (.603 mL, 6.39 mmol, 6.00 eq), and DMAP (ca. 0.01 g) were sequentially added to the crude residue at RT. After stirring overnight, the reaction was quenched with sat. aq. NH_4Cl (35 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 X 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (Hexanes-EtOAc 50:1, then 20:1) gave the metathesis precursor **2.73** (266 mg, 60% over 3 steps) as a yellow oil. ^{1}H NMR (500 MHz, C_6D_6): d 7.78-7.76 (m, 4H), 7.24-7.23 (m, 6H), 5.10-4.98 (m, 1H), 3.57 (t, *J* = 4.97, 4.97 Hz, 2H), 2.25-1.99 (m, 2H), 1.74 (t, *J* = 2.44, 2.44 Hz, 1H), 1.63 (s, 3H), 1.14 (s, 9H), 1.44-1.42 (m, 2H), 1.23-1.27 (m, 2H). ^{13}C (125 MHz, C_6D_6): d 186.35, 136.33, 133.84, 128.94, 83.83, 72.97, 69.50, 64.20, 33.65, 30.90, 28.95, 27.48, 21.02, 15.43. IR (CH_2Cl_2) 3071, 2927, 2856, 1738, 1429, 1373, 1240, 1109 cm^{-1}. LRMS calc'd for $C_{26}H_{34}O_3Si$ (MH^+) 423.2, found 423.2.



(4aR,5aS,9aS,10R,10aR)-2,2-di-*t*-butyl-10-((tert-butyldiphenylsilyl)oxy)-8-methyl-7-vinyl-4a,5a,6,9a,10,10a-hexahydro-4H-pyrano[2',3':5,6]pyrano[3,2][1,3,2]dioxasiline 2.74. A two-necked flask fitted with a condenser was cooled to 0 °C and charged with CH_2Cl_2 (9.14 mL, .007 M) followed by $TiCl_4$ (0.223 mL, 2.05 mmol, 32 eq). To the

resulting solution was added THF (1.09 mL, 12.28 mmol, 192.0 eq) dropwise at which time the solution turned yellow. The addition of THF was followed by the dropwise addition of TMEDA (1.85 mL, 12.28 mmol, 192.0 eq) resulting in the formation of a clear brown solution. The ice bath was removed and the mixture was allowed to stir for 20 min. Activated Zn dust (300 mg, 4.68 mmol, 72.0 eq) and $PbCl_2$ (67.6 mg, 2.43 mmol, 3.80 eq) were then added. The resulting mixture went through a series of color changes from brown to green to purple and finally to blue-green over the course of 3-5 min. To the slurry was transferred a solution of ester **2.67** (40.0 mg, 0.064 mmol, 1.0 eq) and CH_3CHBr_2 (0.186 mL, 2.05 mmol, 32.0 eq) in CH_2Cl_2 (0.90 mL + 0.90 mL rinse, .036 M) via cannula. The reaction mixture was then either heated to reflux for 1.15 h or allowed to stir at rt for 2 h. Following this time period the mixture was cooled to 0 °C and quenched with sat K_2CO_3 (aq., 0.5 mL). After stirring for 30 min at 0 °C, the resulting mixture was filtered through a cotton plug. To the filtrate was added neutral SiO_2 (ca. 100 mg) and was concentrated. The SiO_2 was collected and loaded onto a plug of SiO_2 where it was eluted with 100:1 hexanes-ethyl acetate to give a yellow oil. Flash chromatography (200:1 hexane-ethyl acetate, then 50:1 hexane-ethyl acetate) gave the 1,3-diene **2.74** (26.0 mg, 64%) as an odorless and colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2): d 7.82 (m, 2H), 7.70 (m, 2H), 7.42-7.34 (m, 6H), 6.42 (dd, 17.09, 10.74 Hz, 2H), 4.81 (dd, *J* = 17.09, 0.97 Hz, 1H), 4.73 (d, *J* = 10.79), 4.13-4.09 (m, 1H), 4.00 (t, *J* = 8.79, 8.79 Hz, 1H), 3.73 (t, *J* = 10.25, 10.25 Hz, 1H), 3.47 (t, *J* = 9.76, 9.76 Hz, 1H), 3.40-3.31 (m, 2H), 2.35 (dd, *J* = 15.14, 5.37 Hz, 1H), 2.00 (m, 1H), 1.18 (s, 3H), 1.08 (s, 9H), 1.06 (s, 9H), 0.98 (s, 9H). ^{13}C (125 MHz, CD_2Cl_2): d 137.02, 136.30, 134.40, 130.07, 129.51, 127.98, 127.59, 127.53, 107.83, 105.85, 79.38, 78.62, 77.70, 75.48, 73.11, 66.94, 30.25, 28.11,

27.90, 27.34, 27.31, 23.17, 20.31, 15.27. IR (CD_2Cl_2) 3071, 2933, 2859, 1642, 1472, 1428, 1387, 1166, 1112, 1051, 827 cm^{-1}. LRMS calc'd for $C_{26}H_{34}O_3Si$ (MH^+) 621.1, found 621.1.

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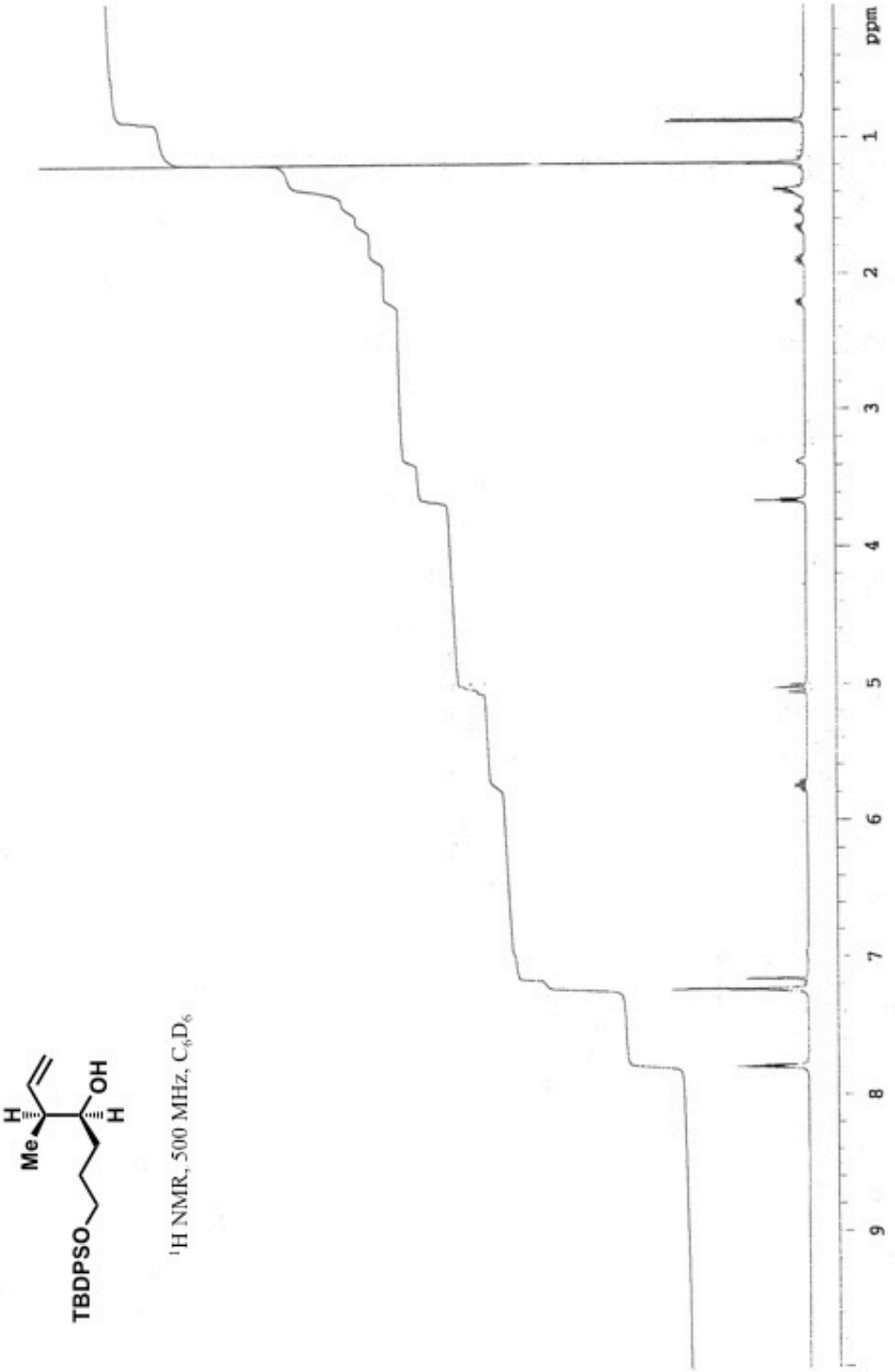
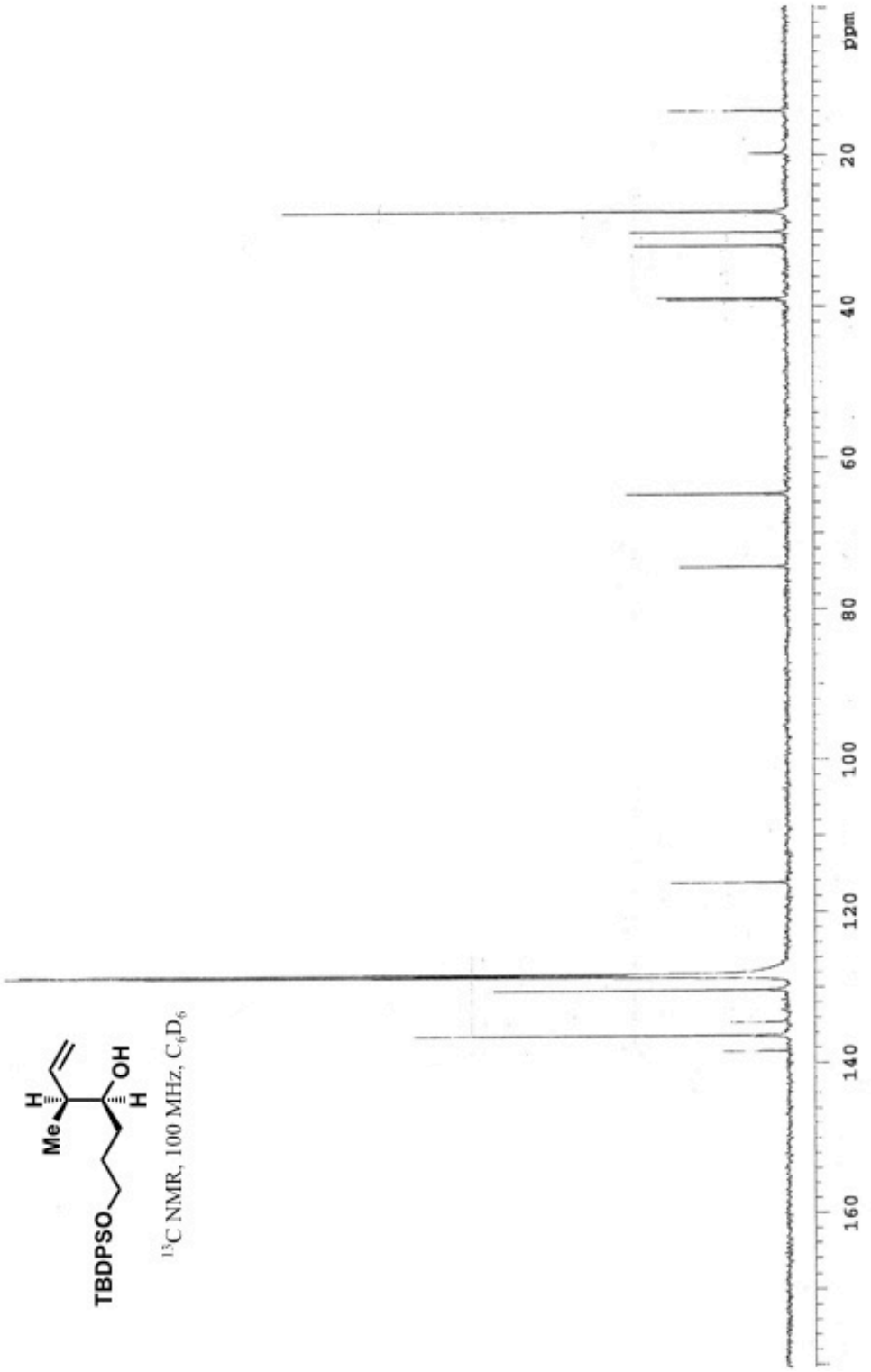
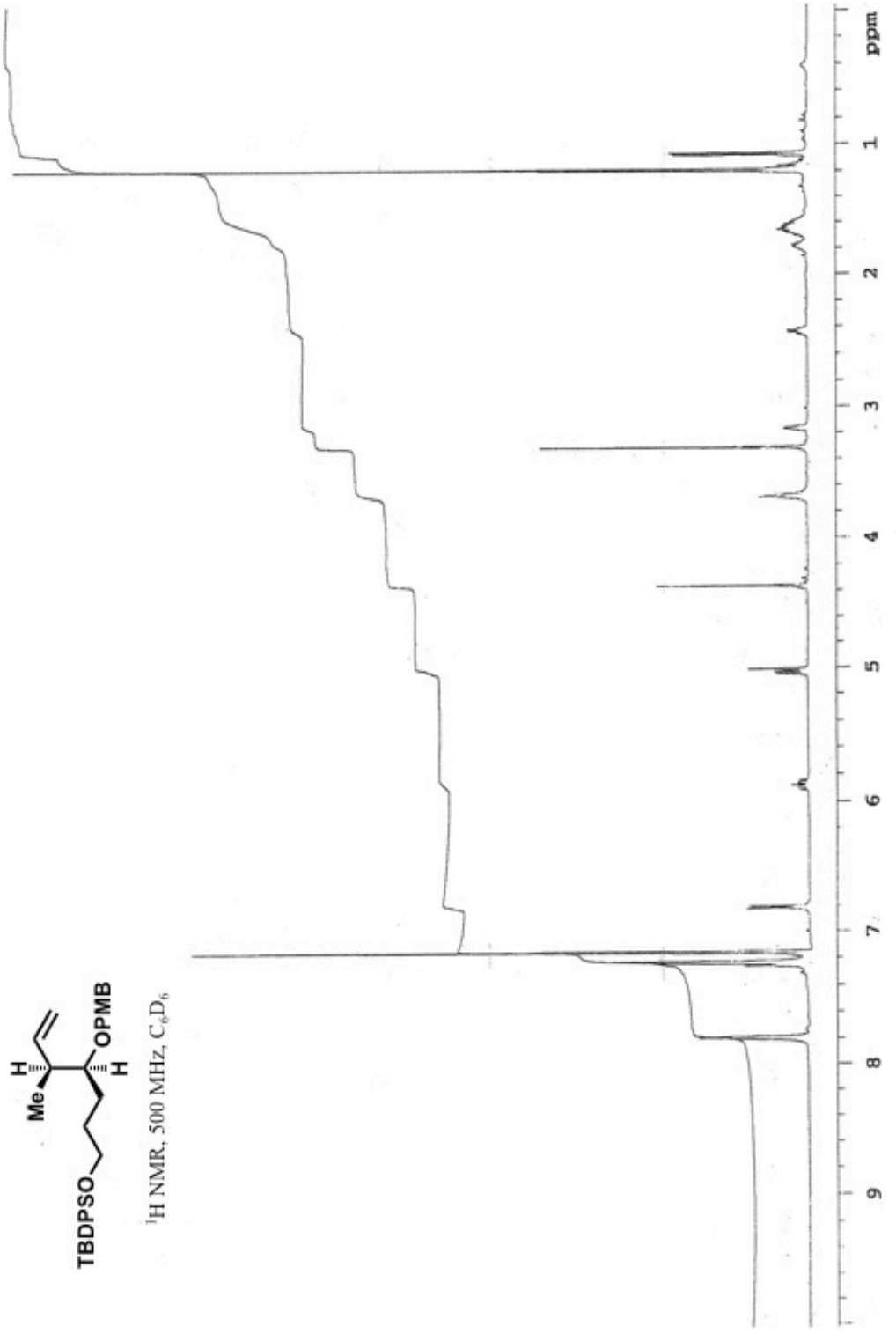
APPENDIX A: ^{1}H, AND ^{13}C NMR SPECTRA CHAPTER 1



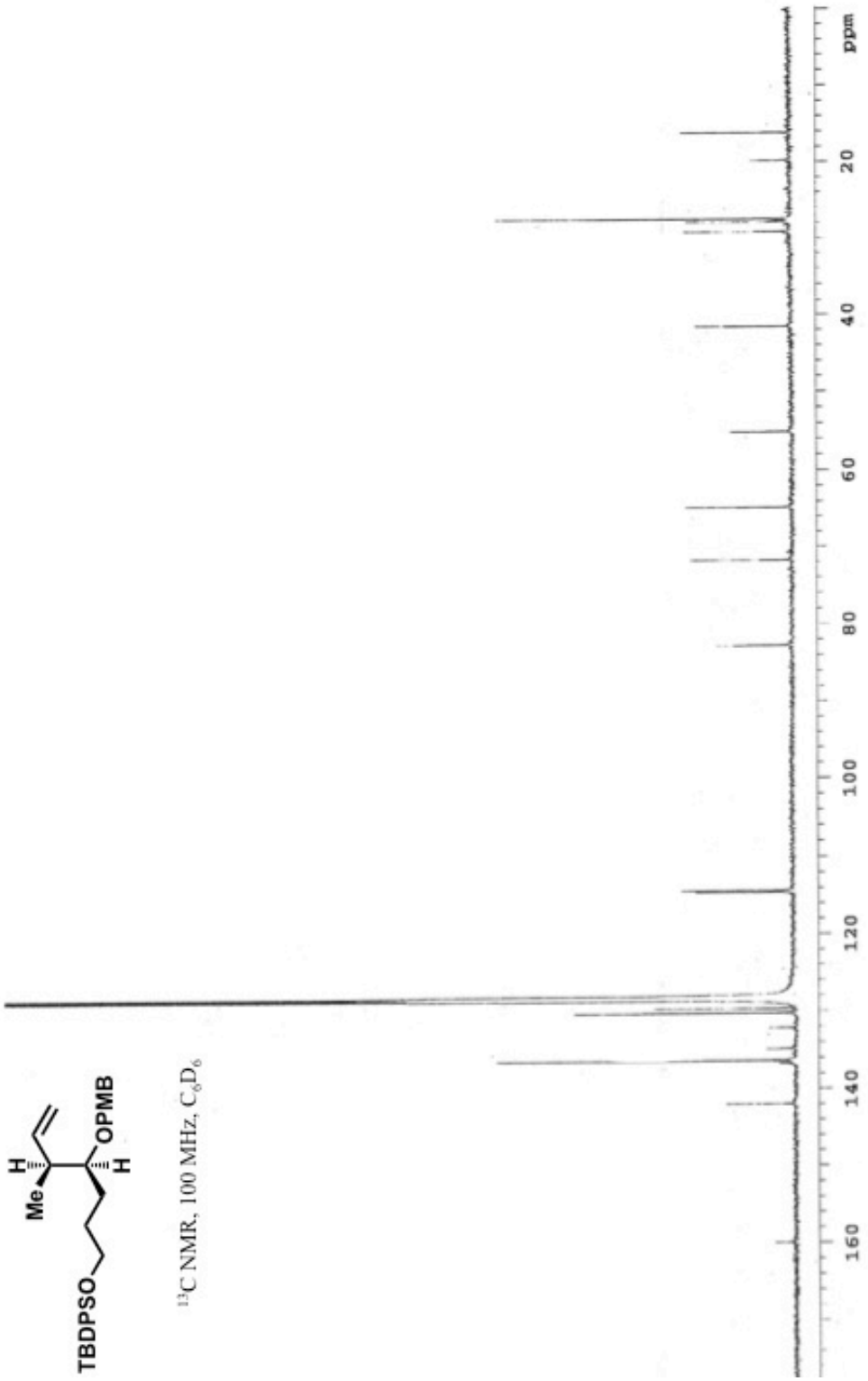
^{1}H NMR, 500 MHz, C_6D_6



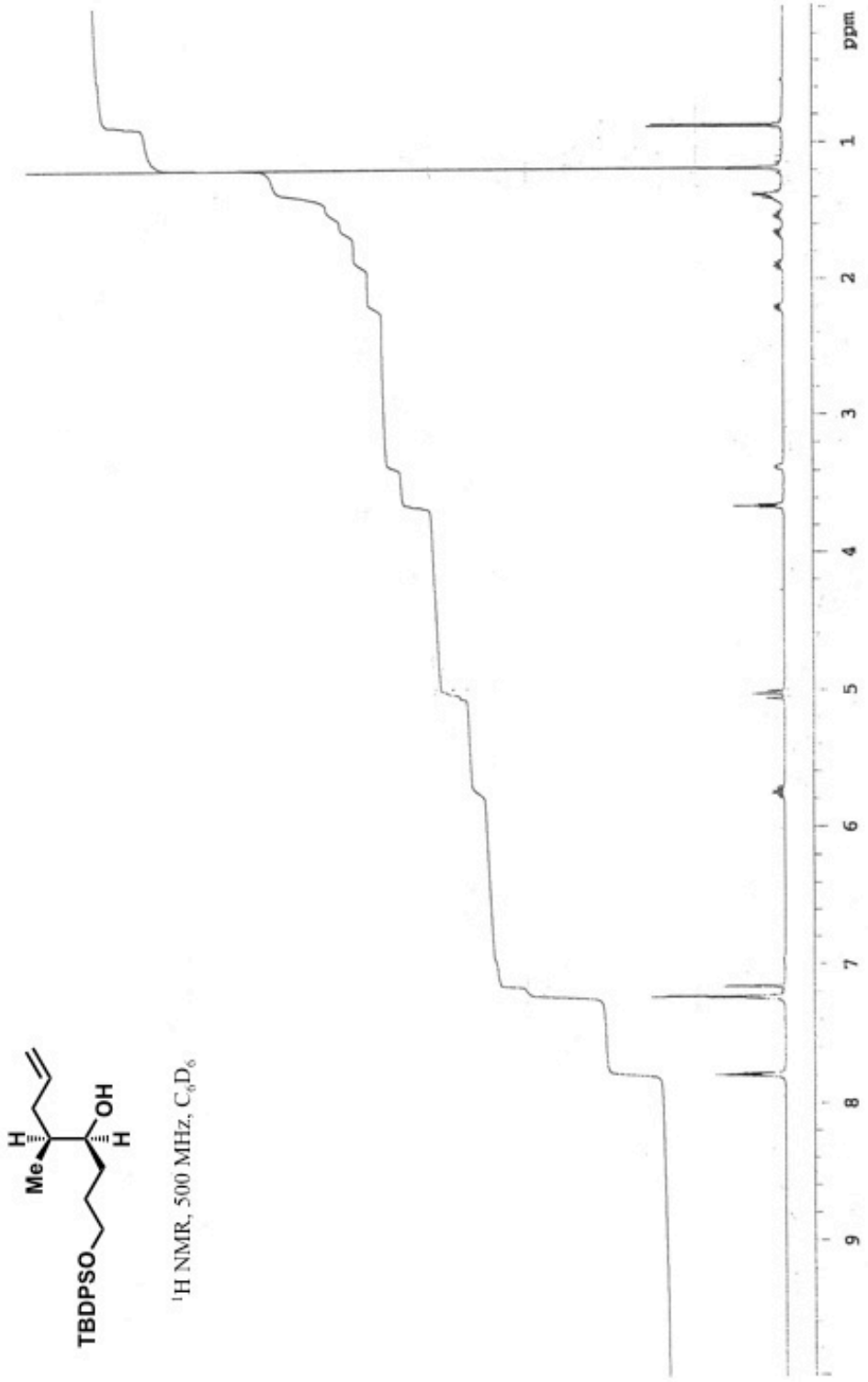
^{13}C NMR, 100 MHz, C_6D_6



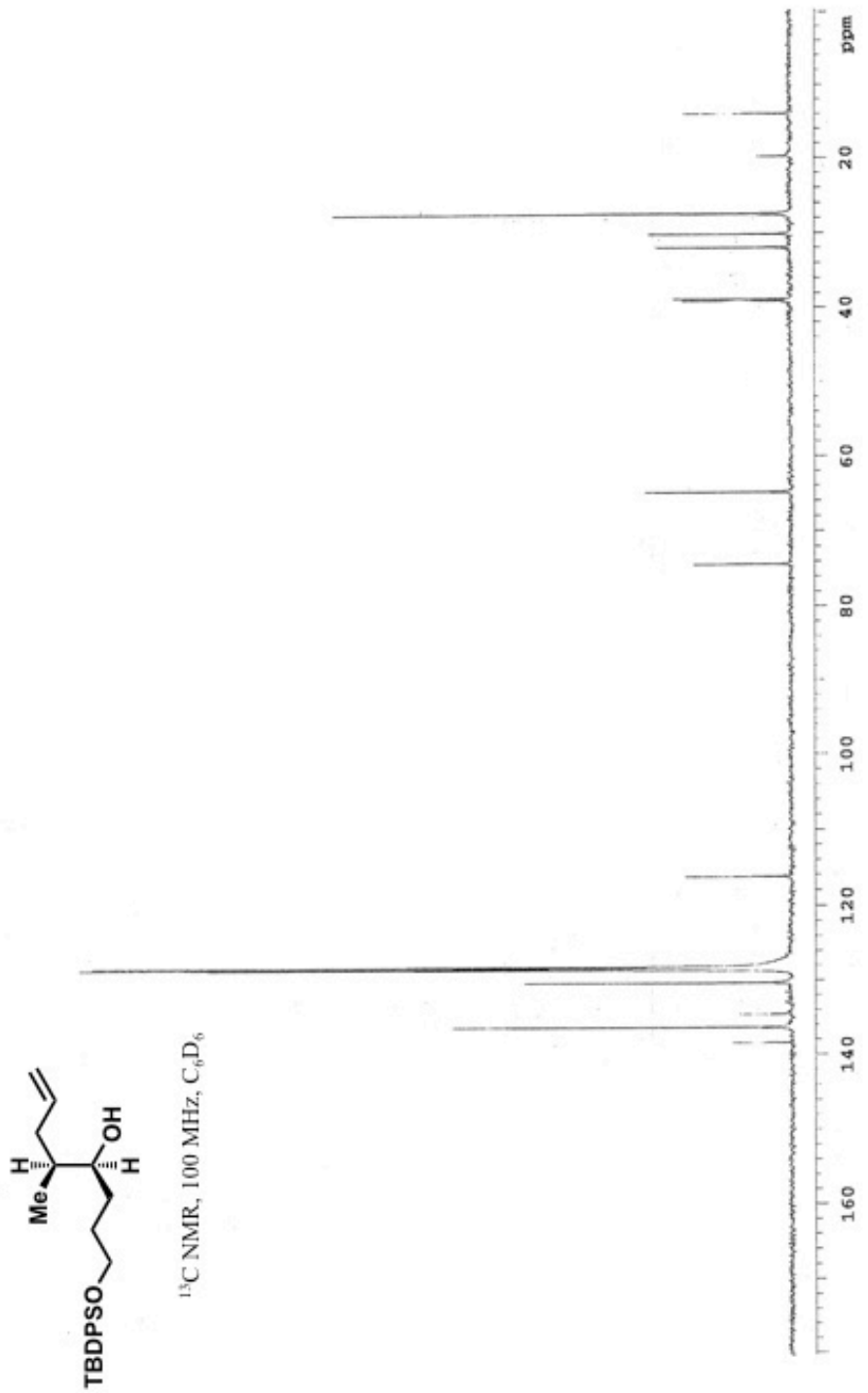
^{1}H NMR, 500 MHz, C_6D_6



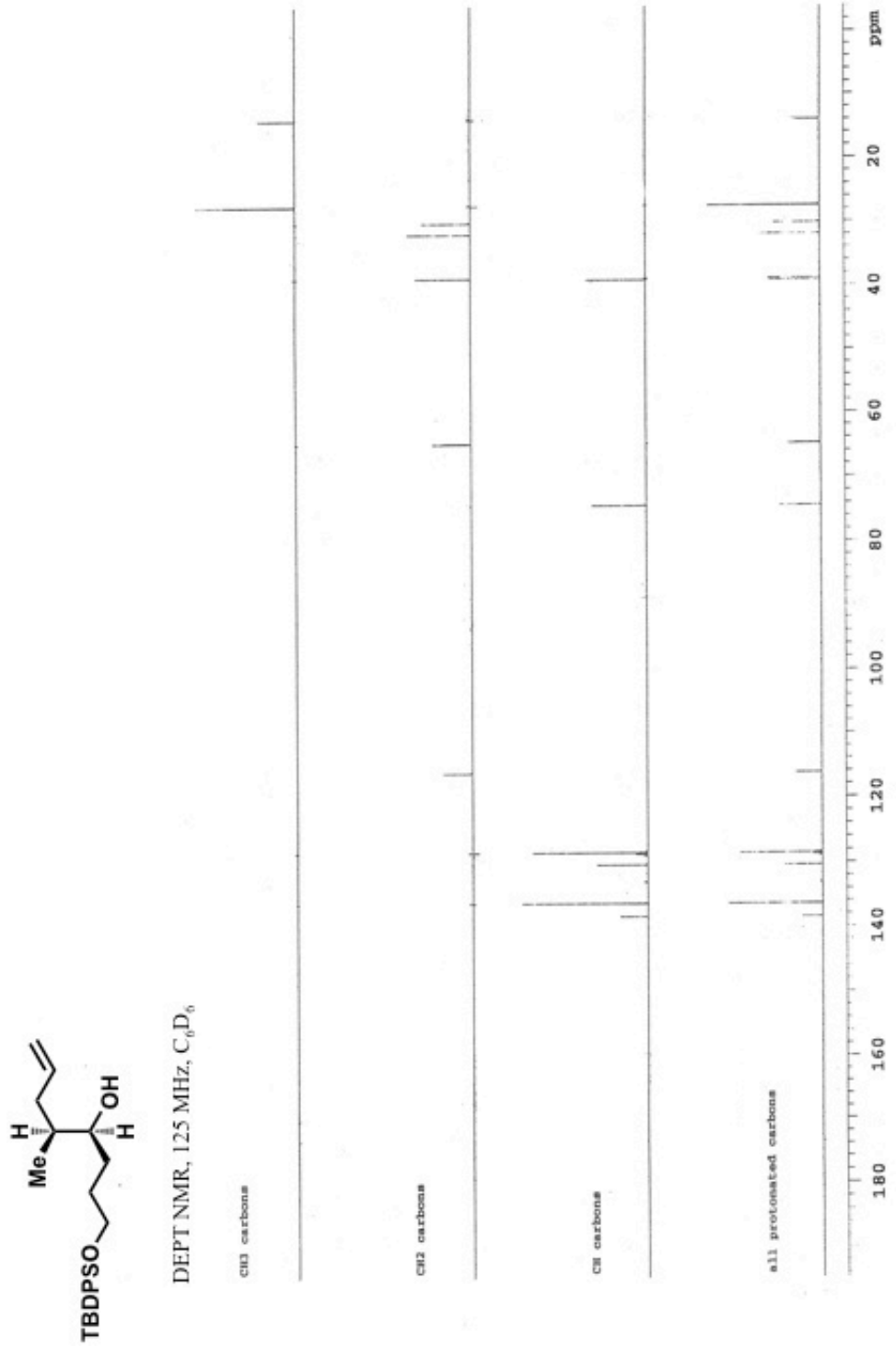
^{13}C NMR, 100 MHz, C_6D_6

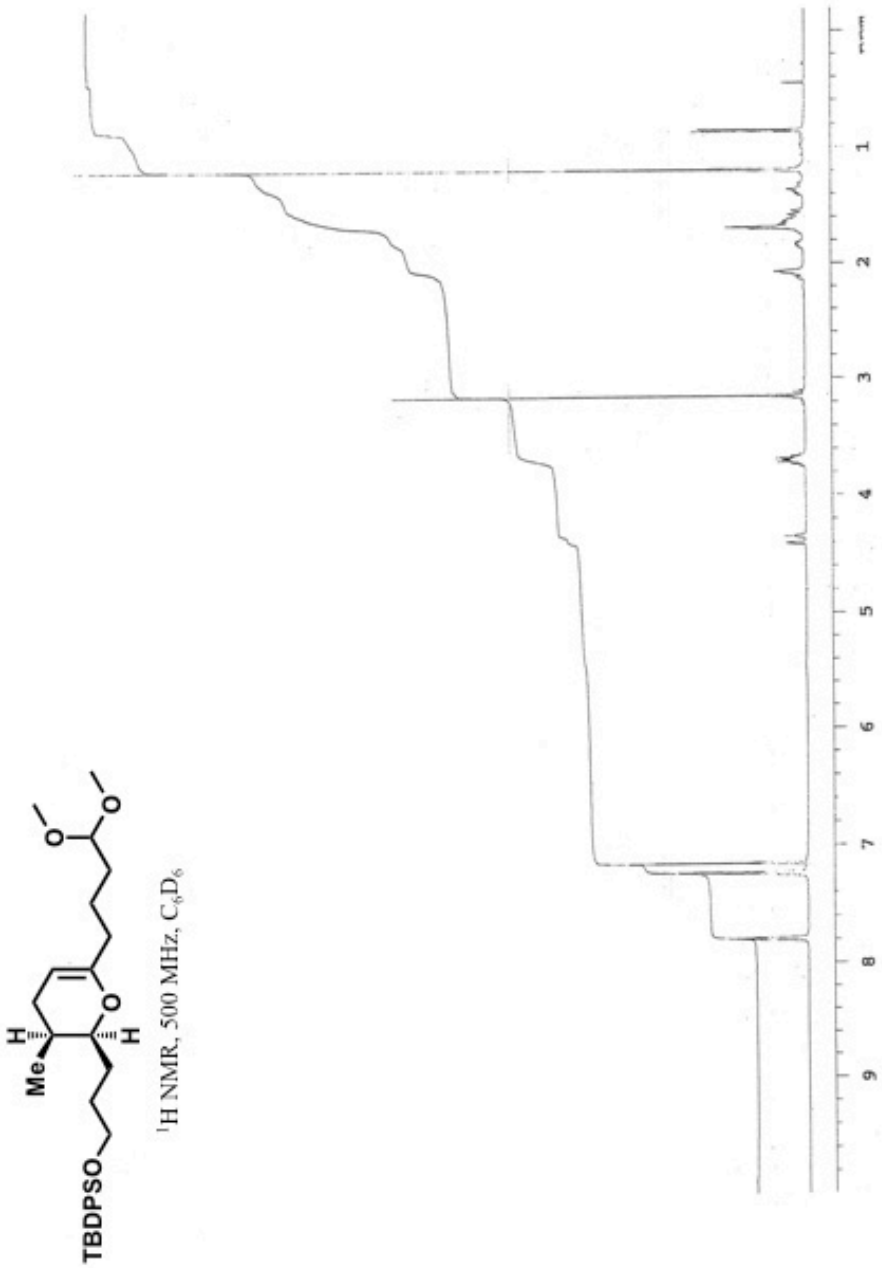


^{1}H NMR, 500 MHz, C_6D_6

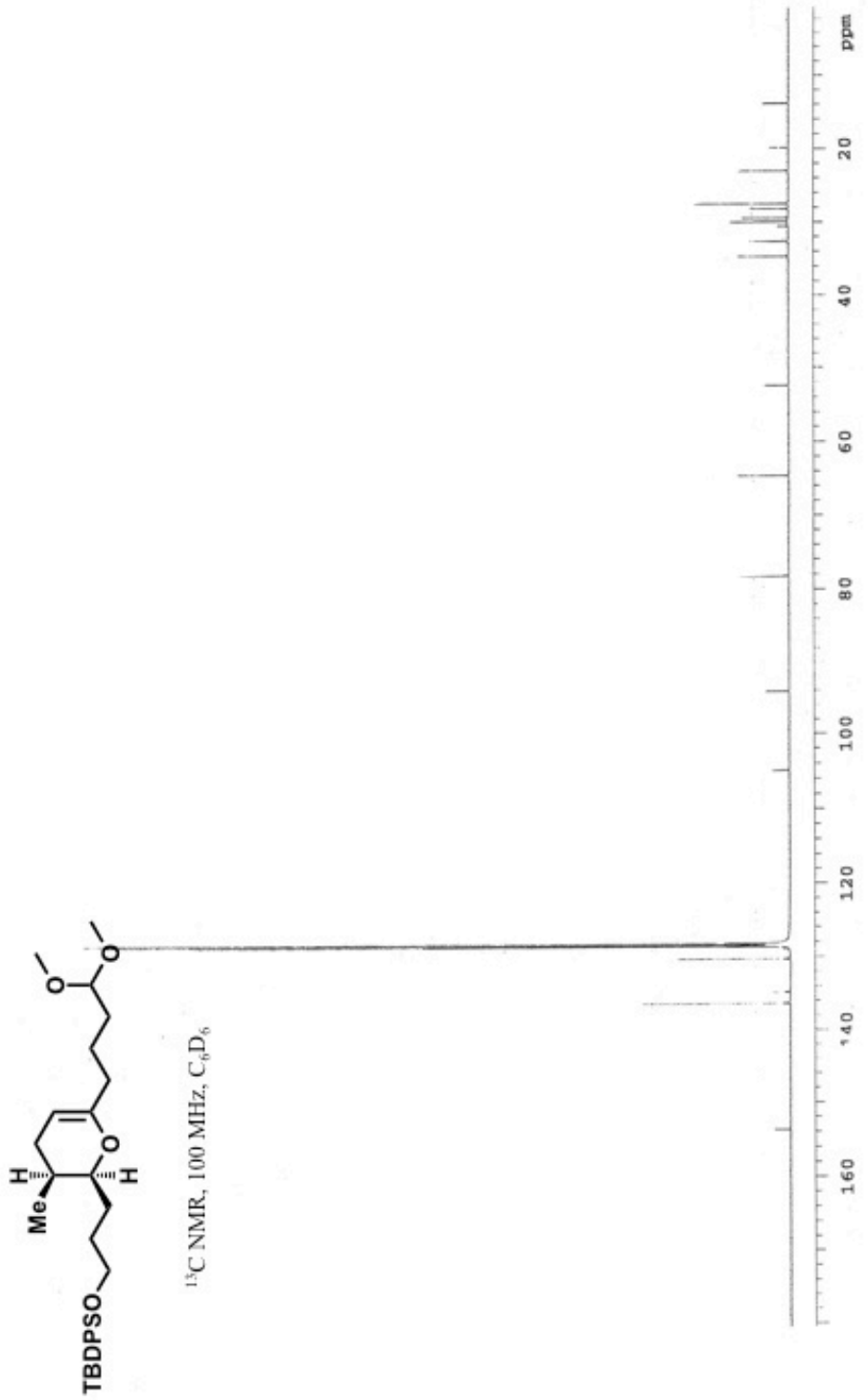


^{13}C NMR, 100 MHz, C_6D_6


TBDPSO
Me
H
OH
H
DEPT NMR, 125 MHz, C6D6
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
180
160
140
120
100
80
60
40
20
ppm

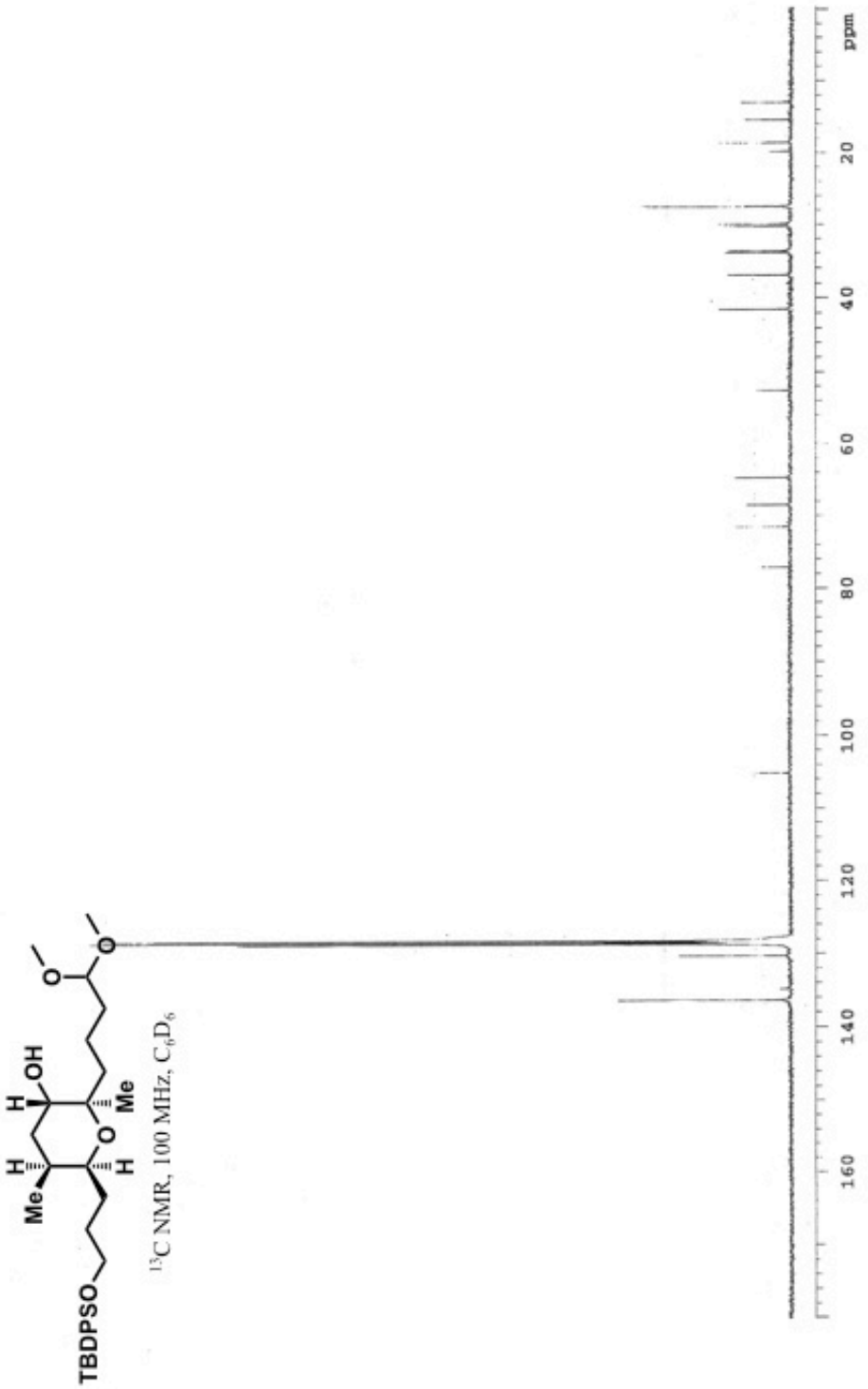


^{1}H NMR, 500 MHz, C_6D_6



^{13}C NMR, 100 MHz, C_6D_6

^{1}H NMR, 500 MHz, C_6D_6



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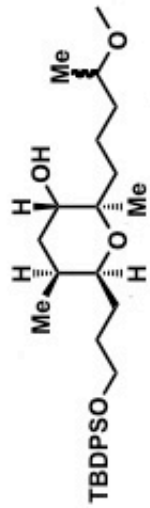

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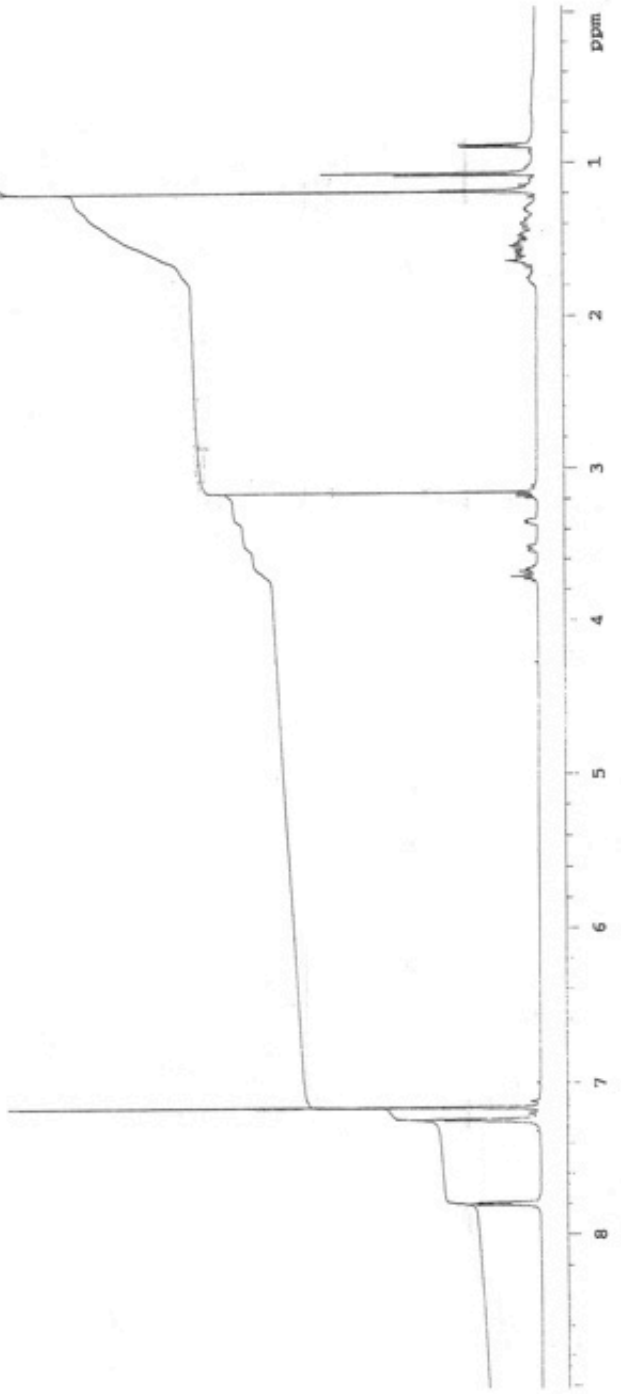
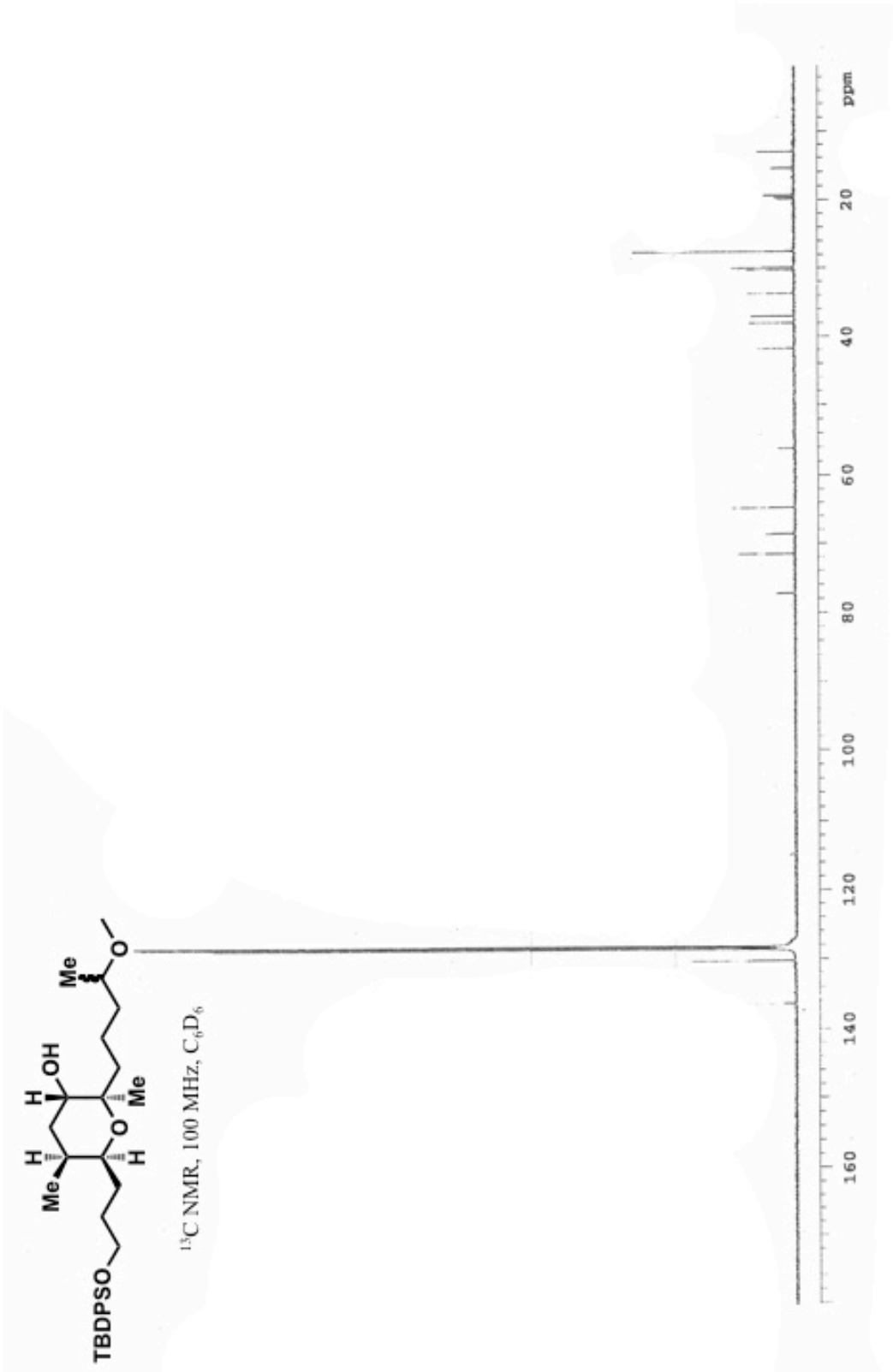
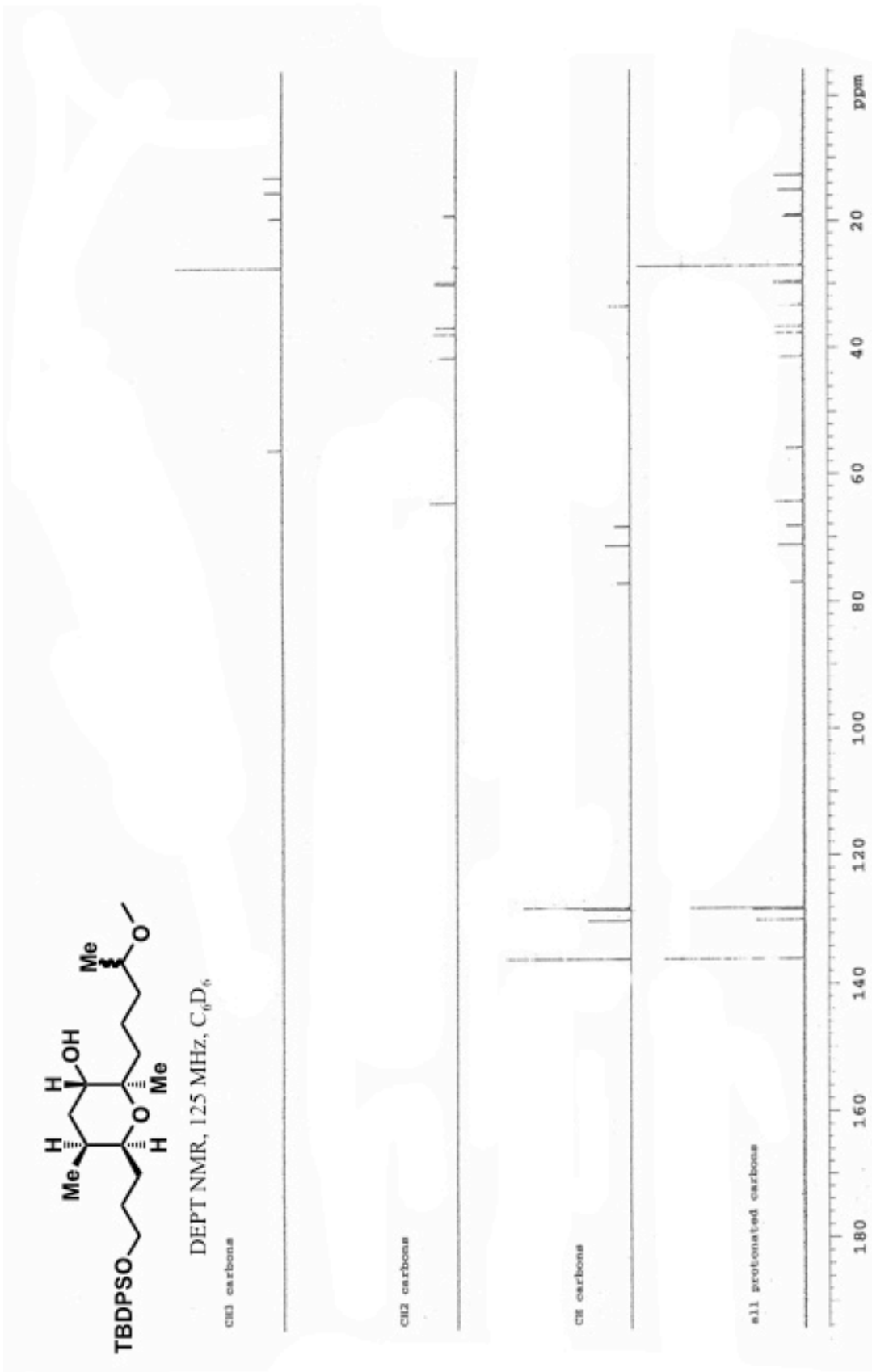
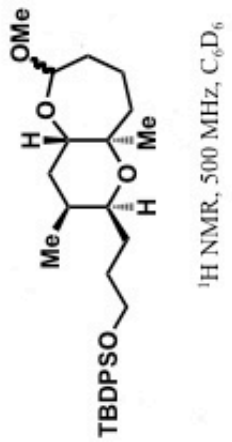
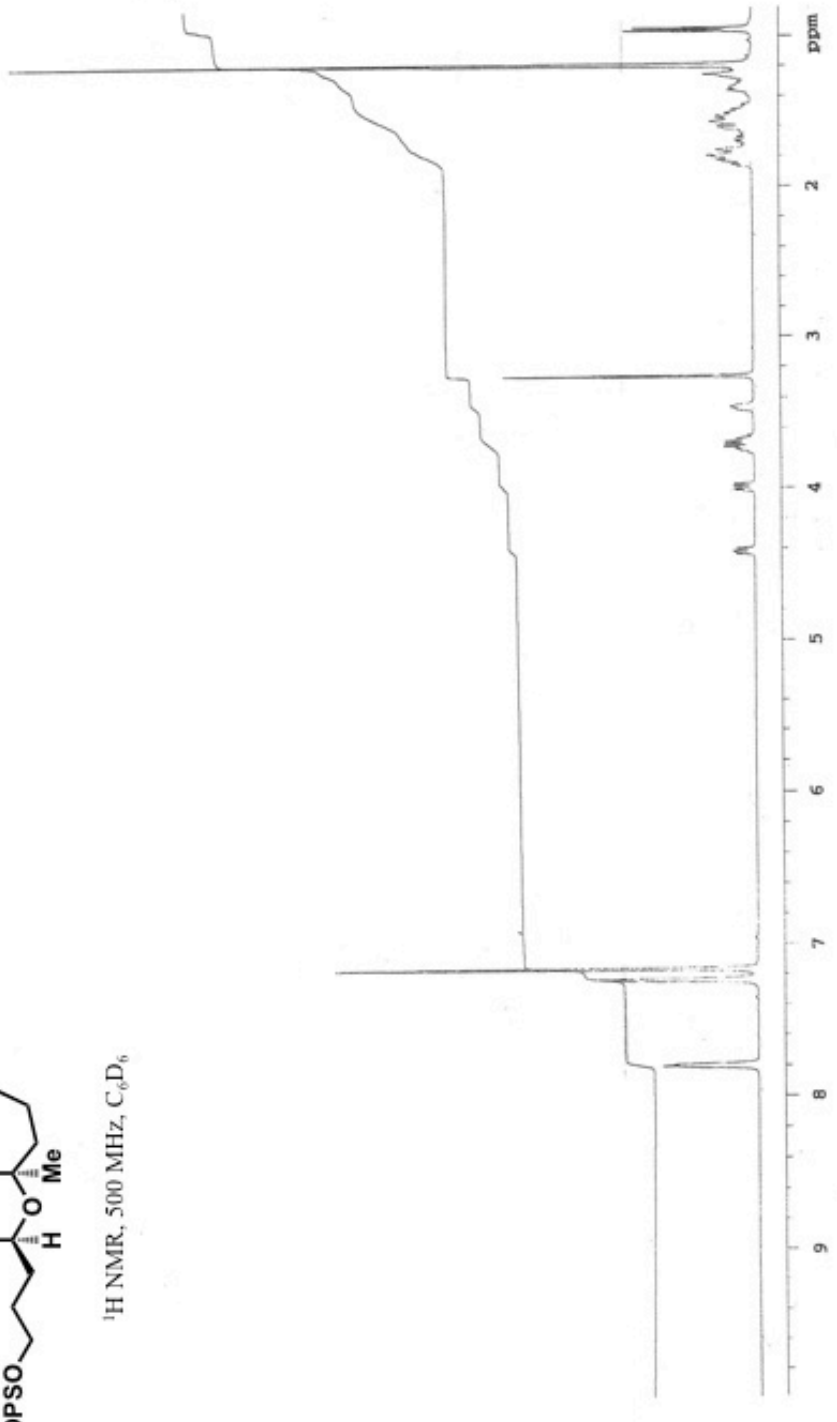


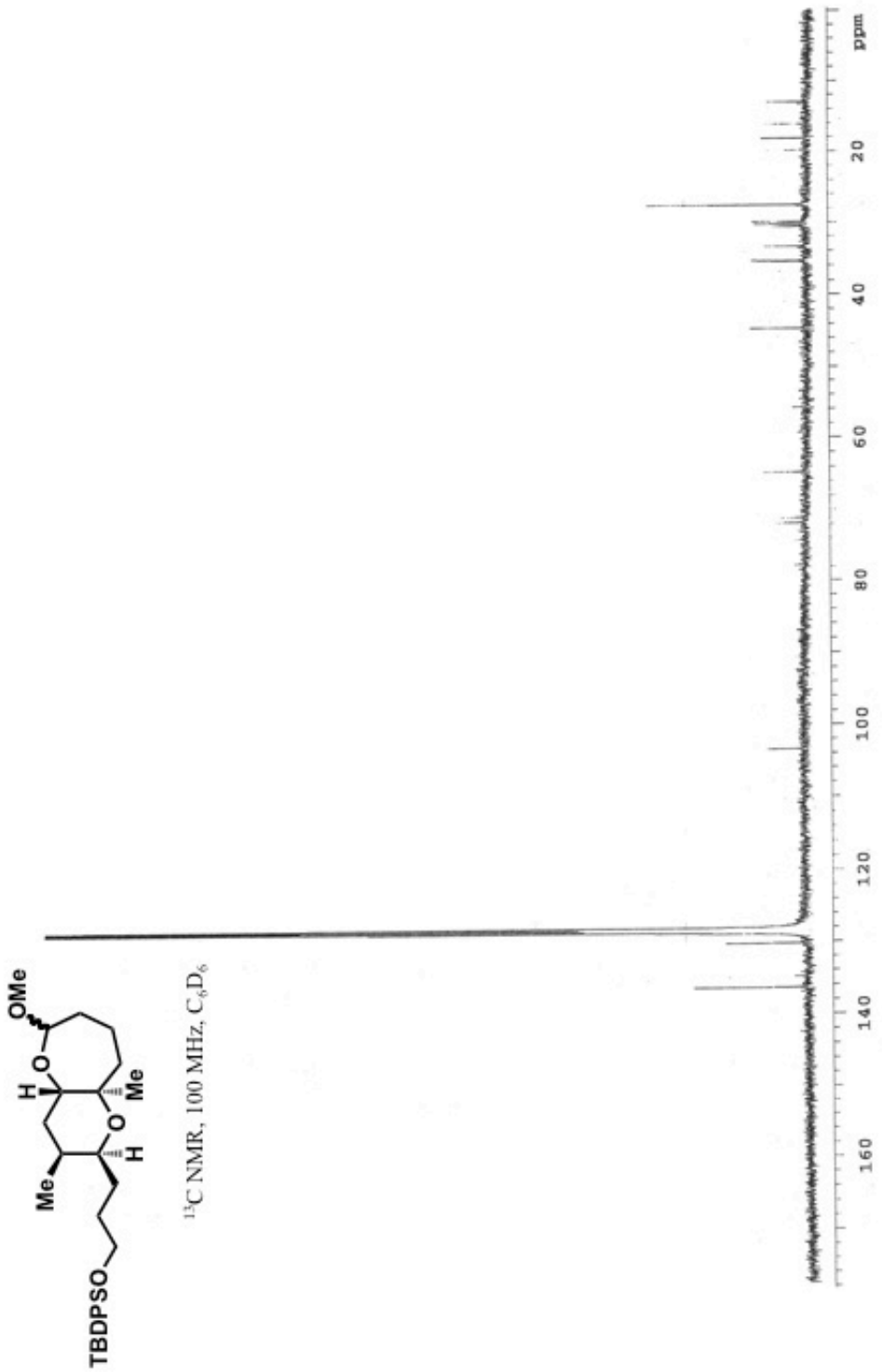

TBDPSO
Me
H
OH
H
Me
O
O
H
Me
Me
O
^{13}C NMR, 100 MHz, C_6D_6
160
140
120
100
80
60
40
20
ppm


TBDPSO
Me
H
OH
Me
H
O
H
Me
O
DEPT NMR, 125 MHz, C_6D_6
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
180
160
140
120
100
80
60
40
20
ppm



^{1}H NMR, 500 MHz, C_6D_6





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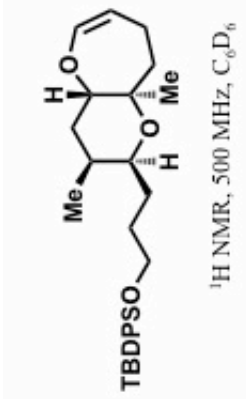
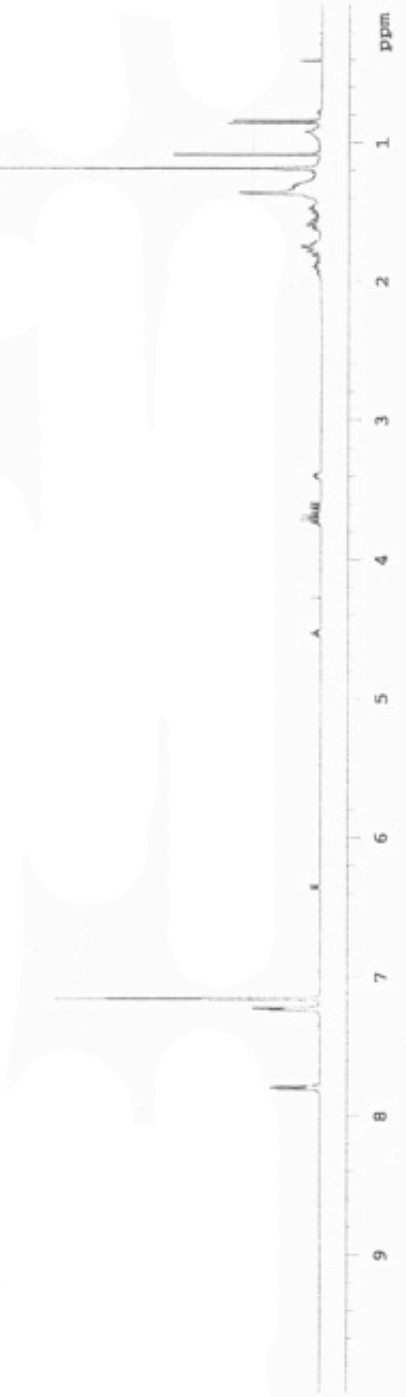
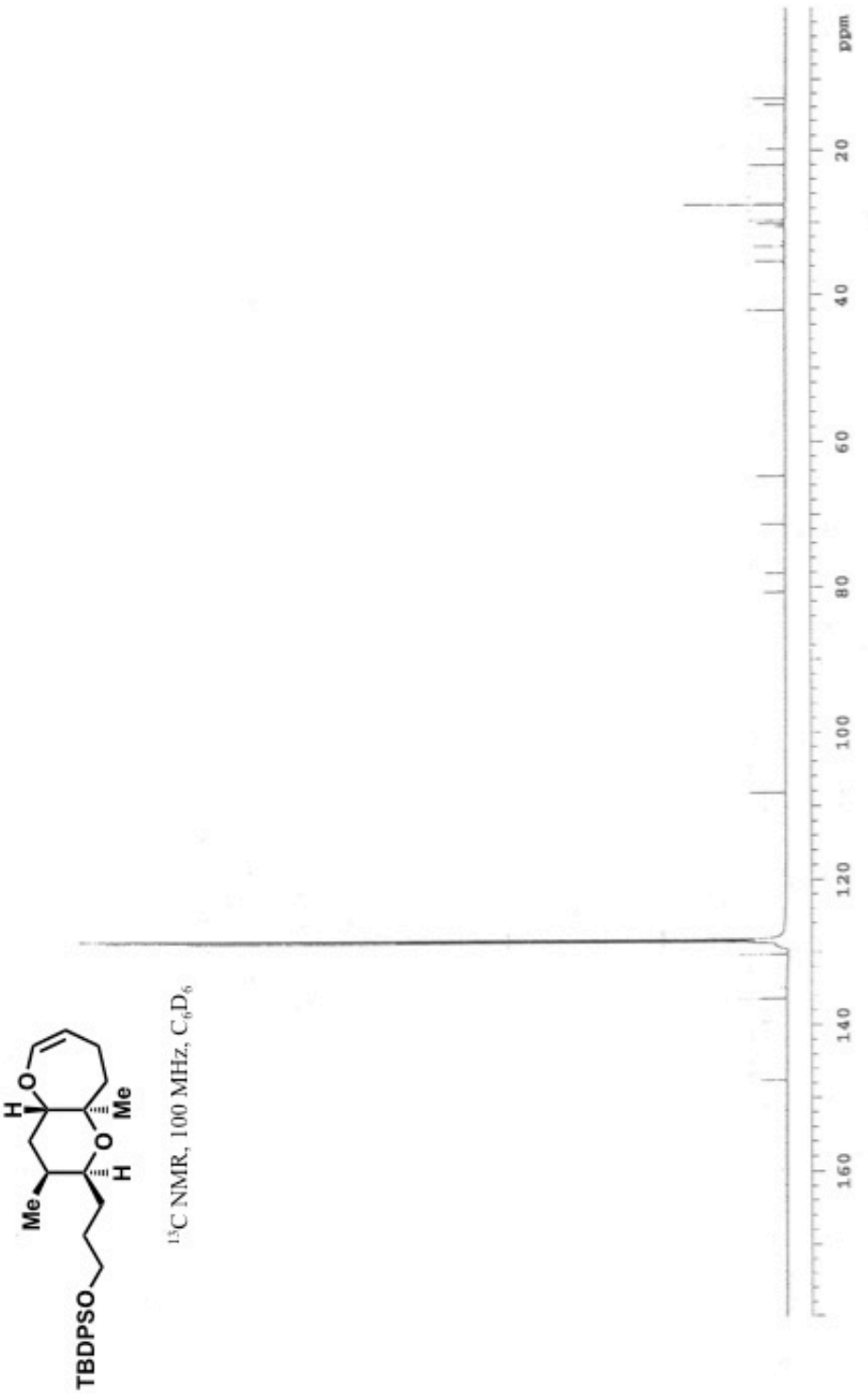
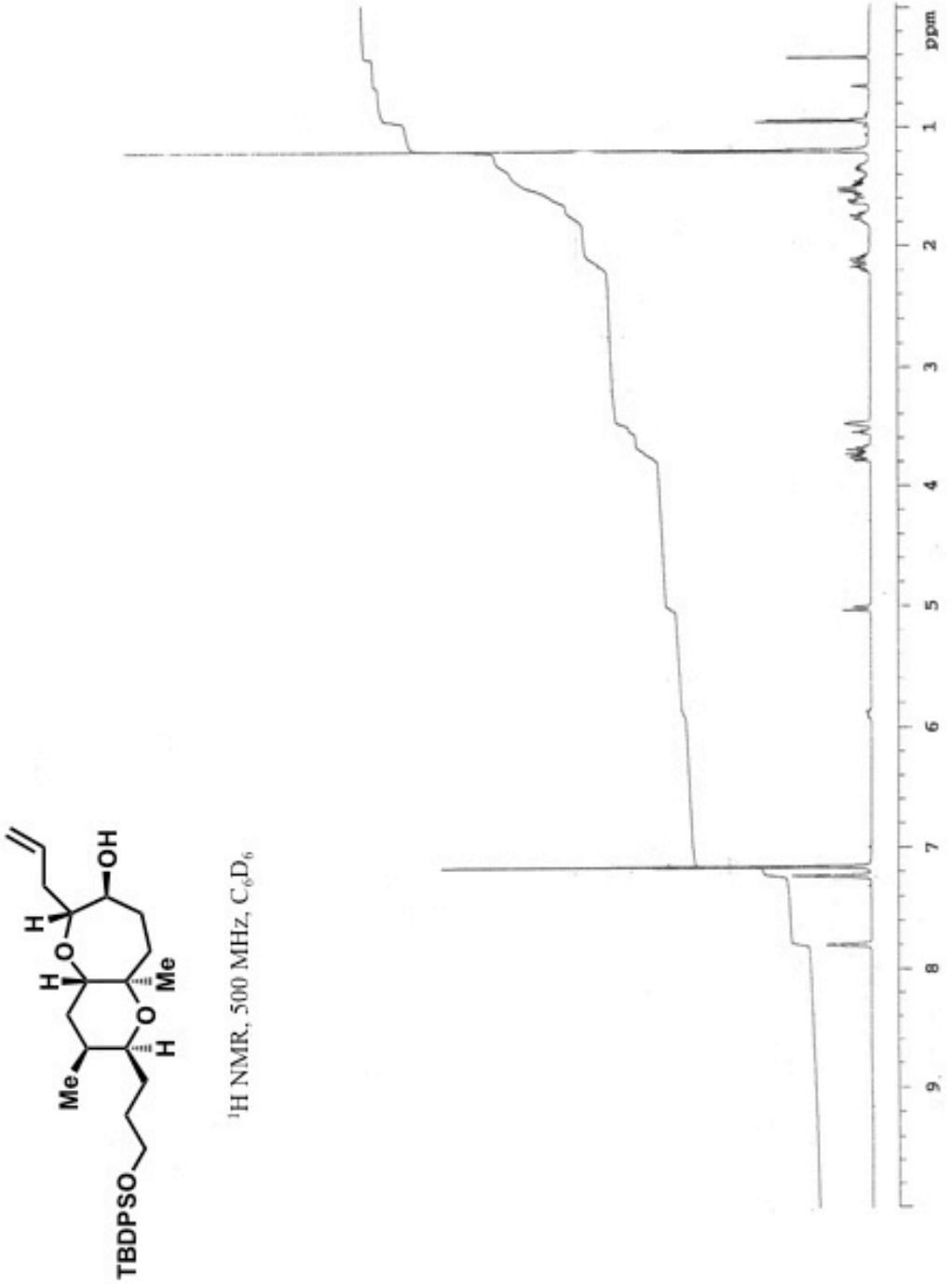


^{1}H NMR, 500 MHz, C_6D_6





^{13}C NMR, 100 MHz, C_6D_6



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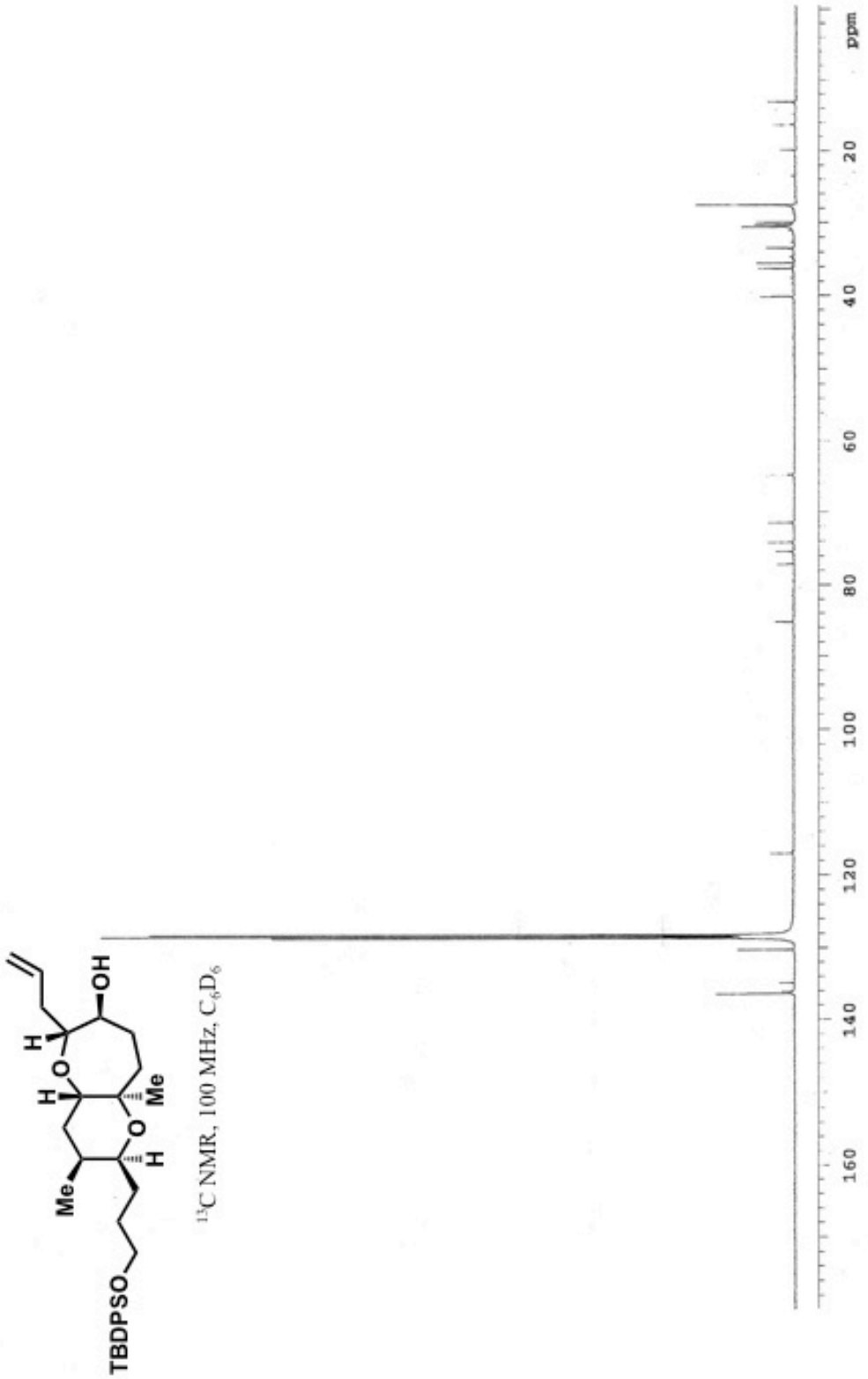
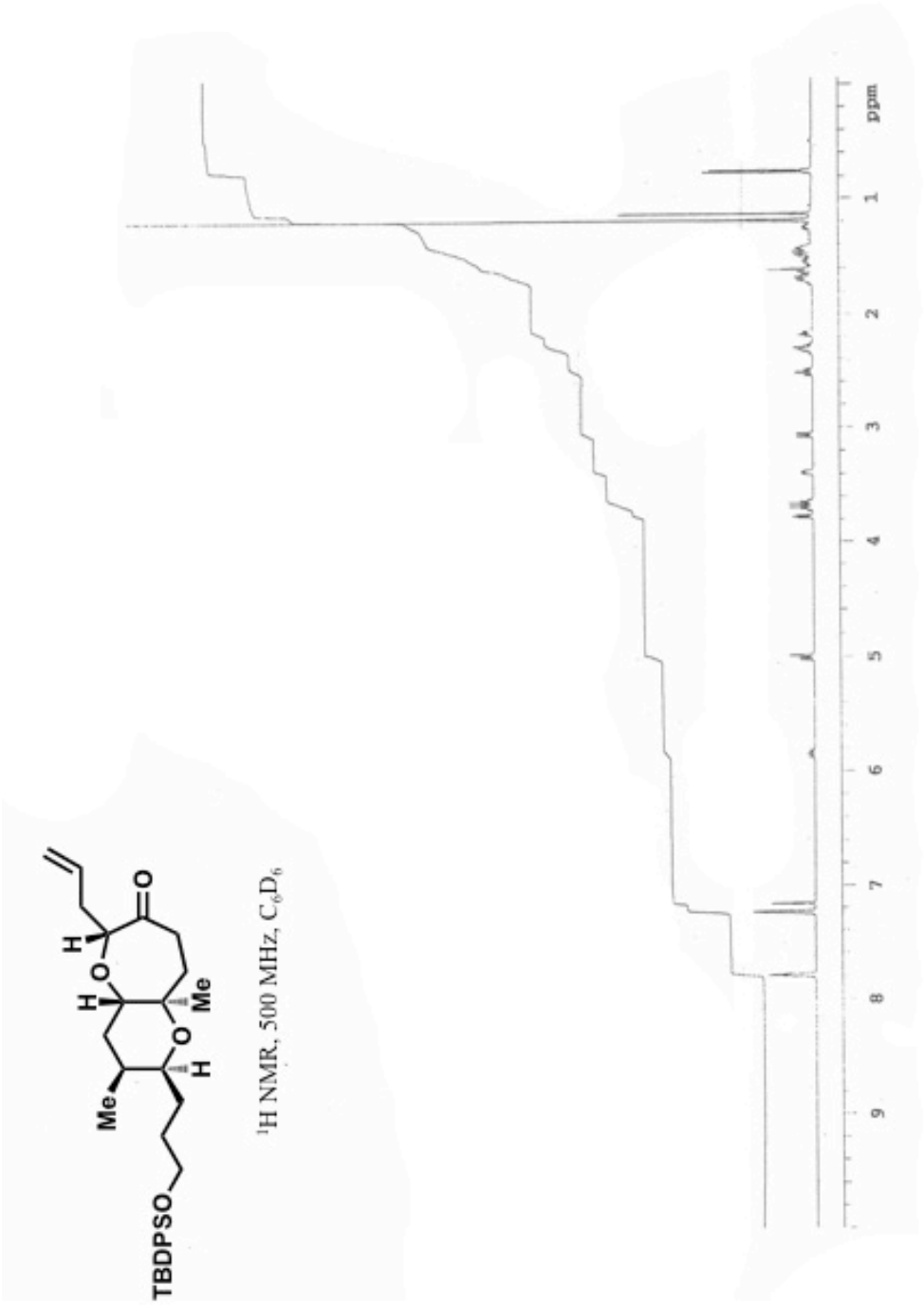
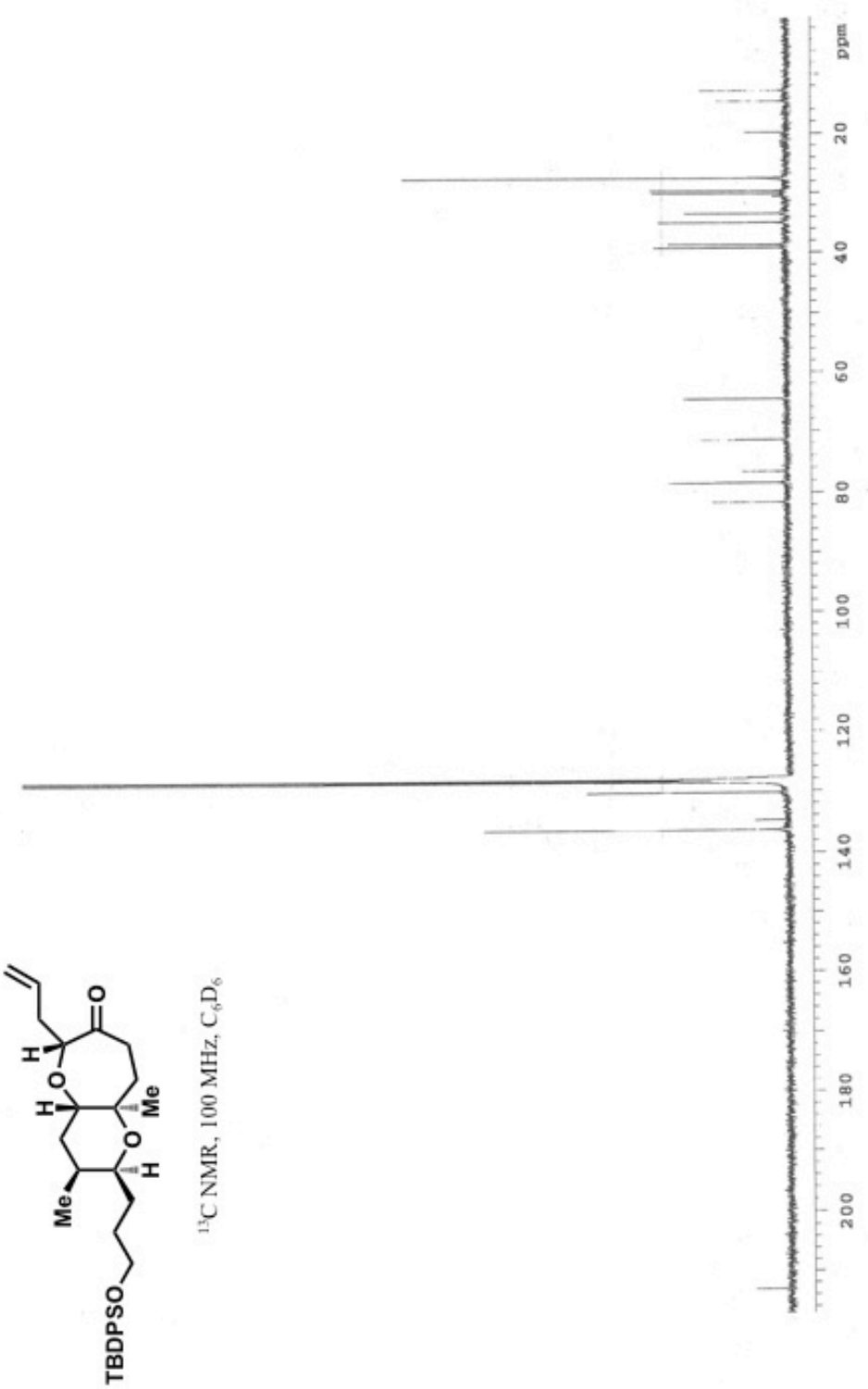
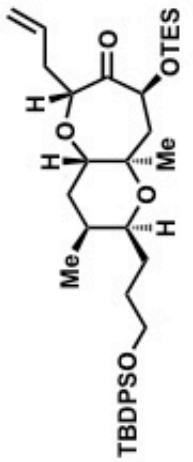


^{13}C NMR, 100 MHz, C_6D_6

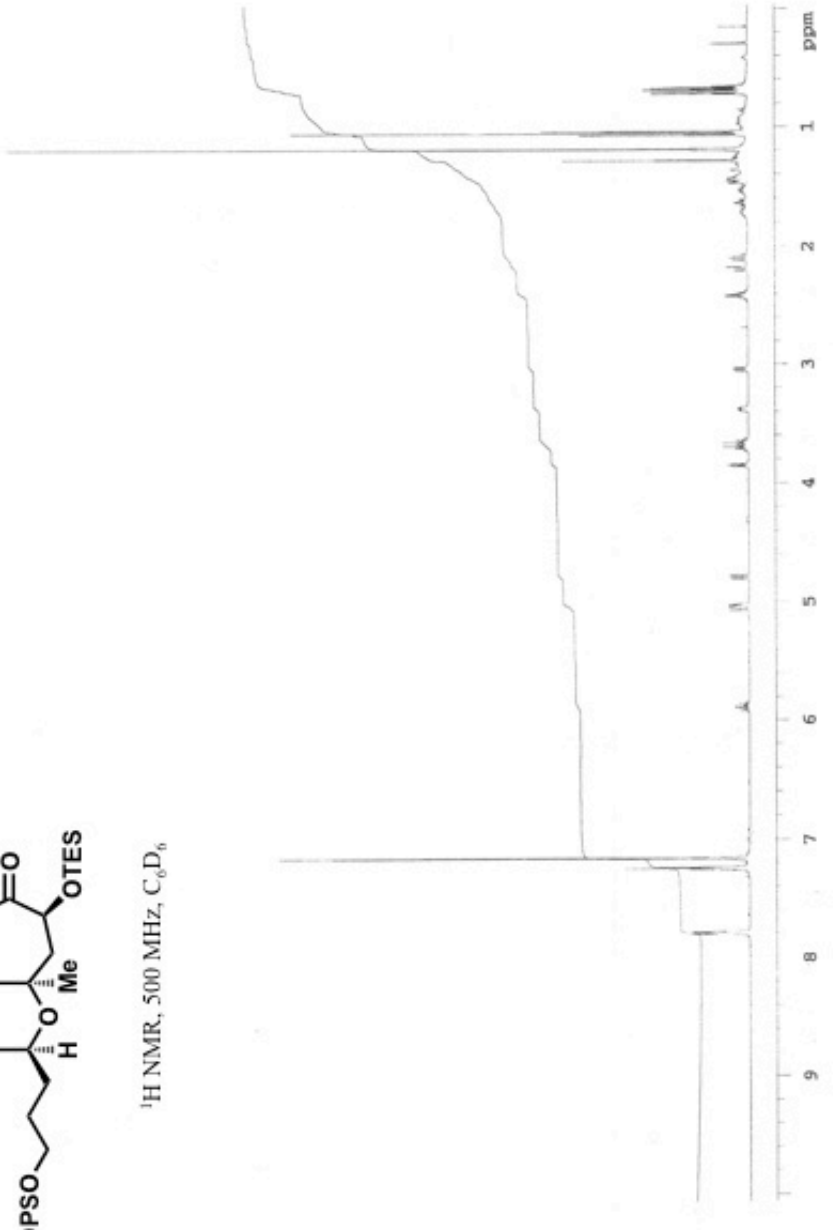

TBDPSO
Me
Me
H
O
O
O
H
H
O
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8
9

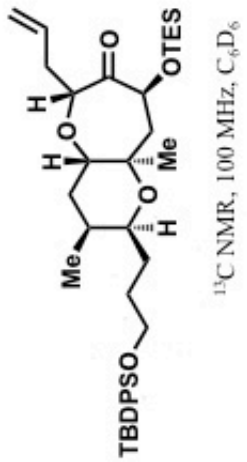


^{13}C NMR, 100 MHz, C_6D_6

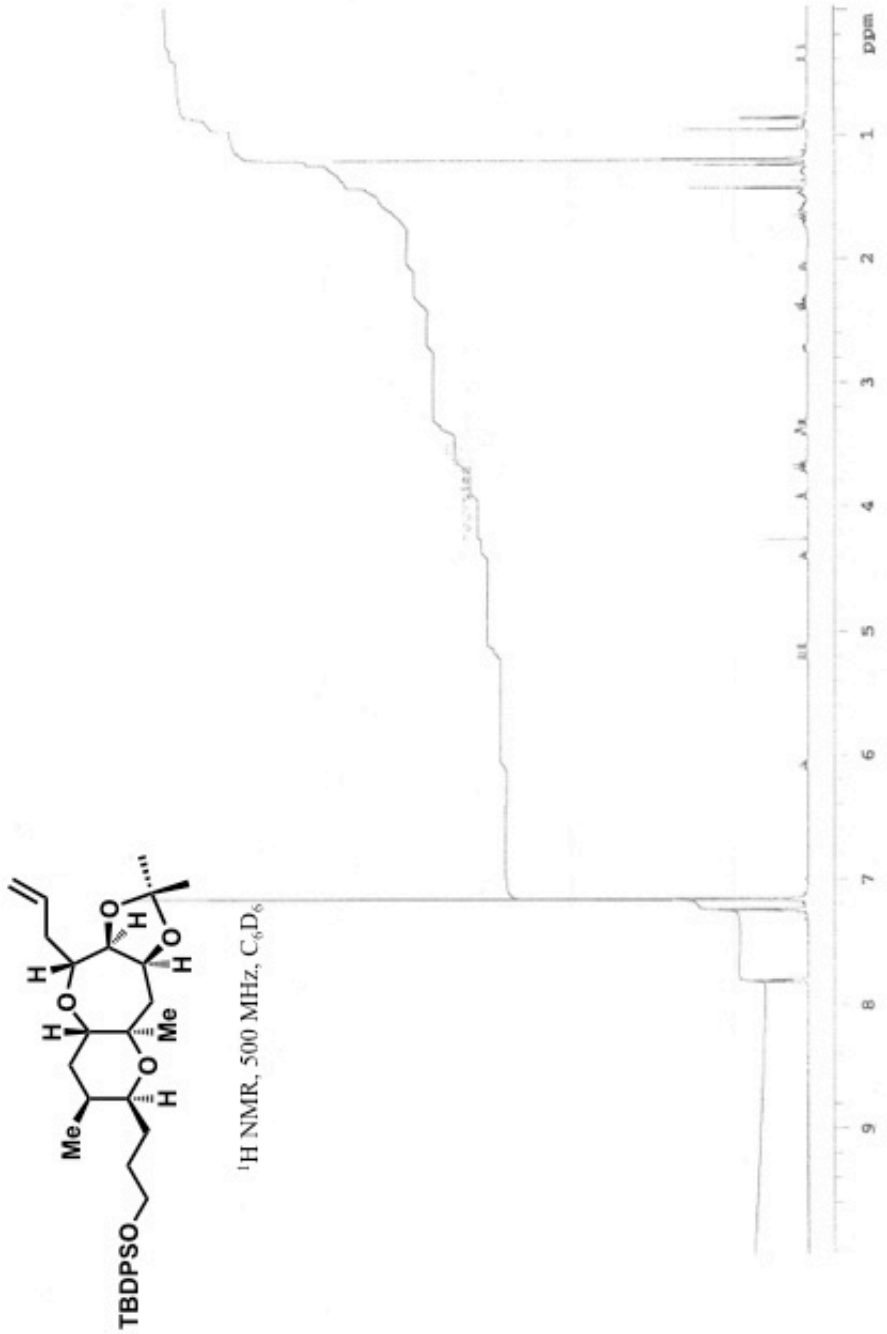


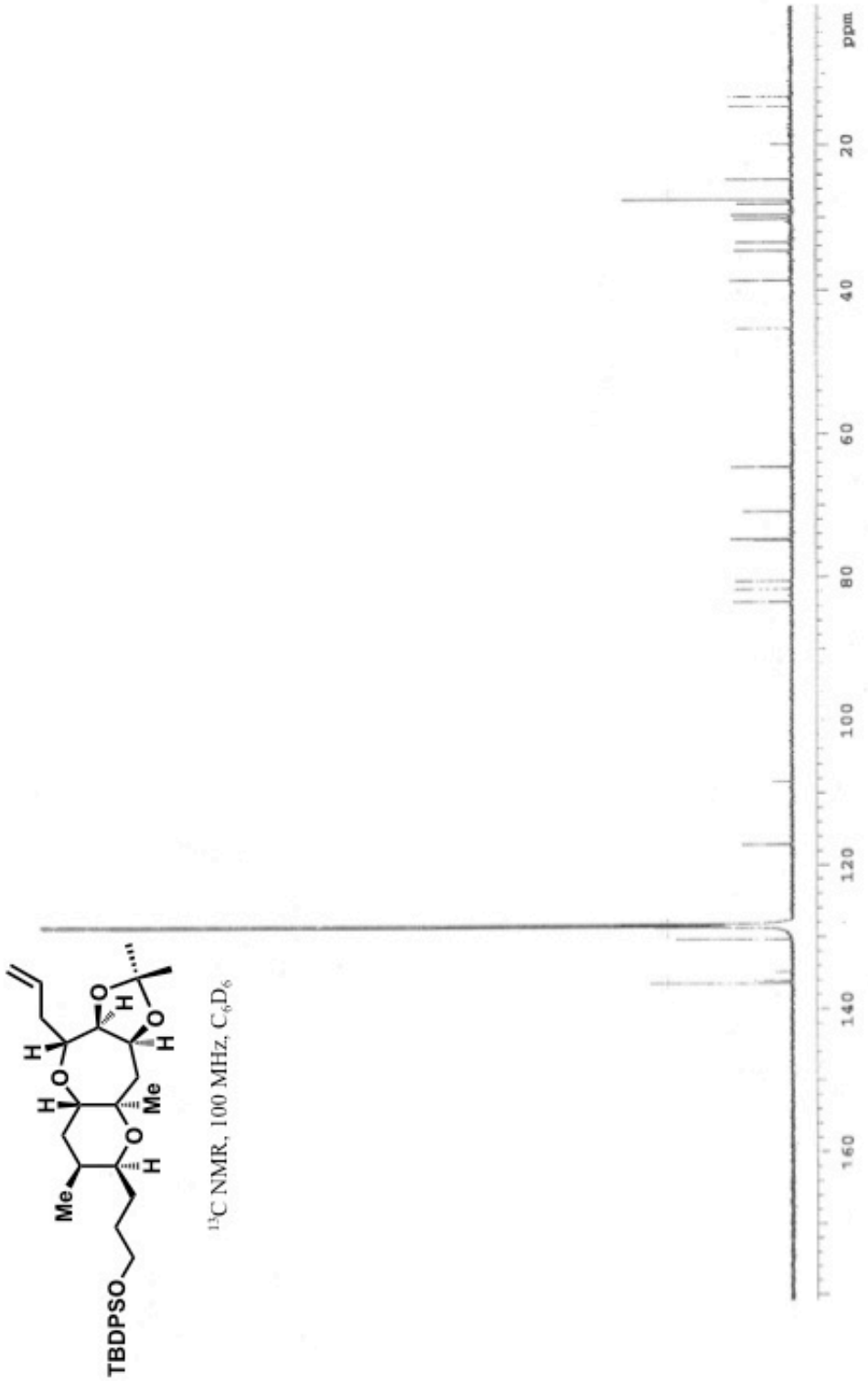
^{1}H NMR, 500 MHz, C_6D_6



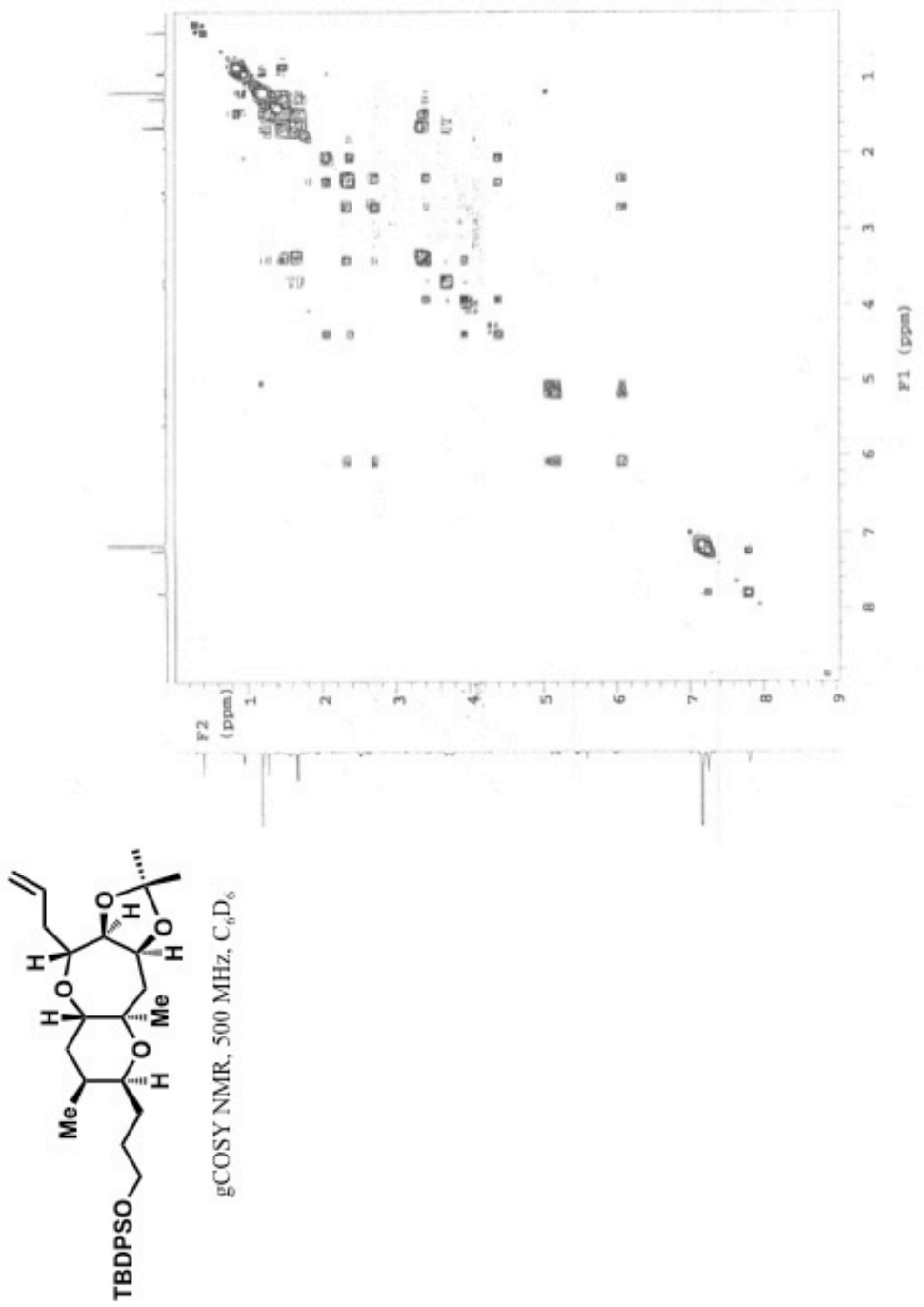


^{13}C NMR, 100 MHz, C_6D_6

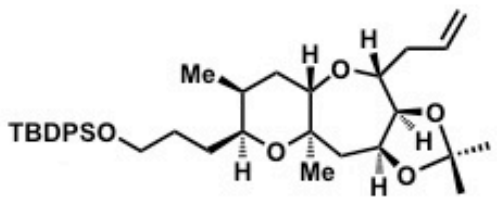

TBDPSO
Me
Me
H
O
H
O
H
O
H
O
H
O
^{1}H NMR, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8
9



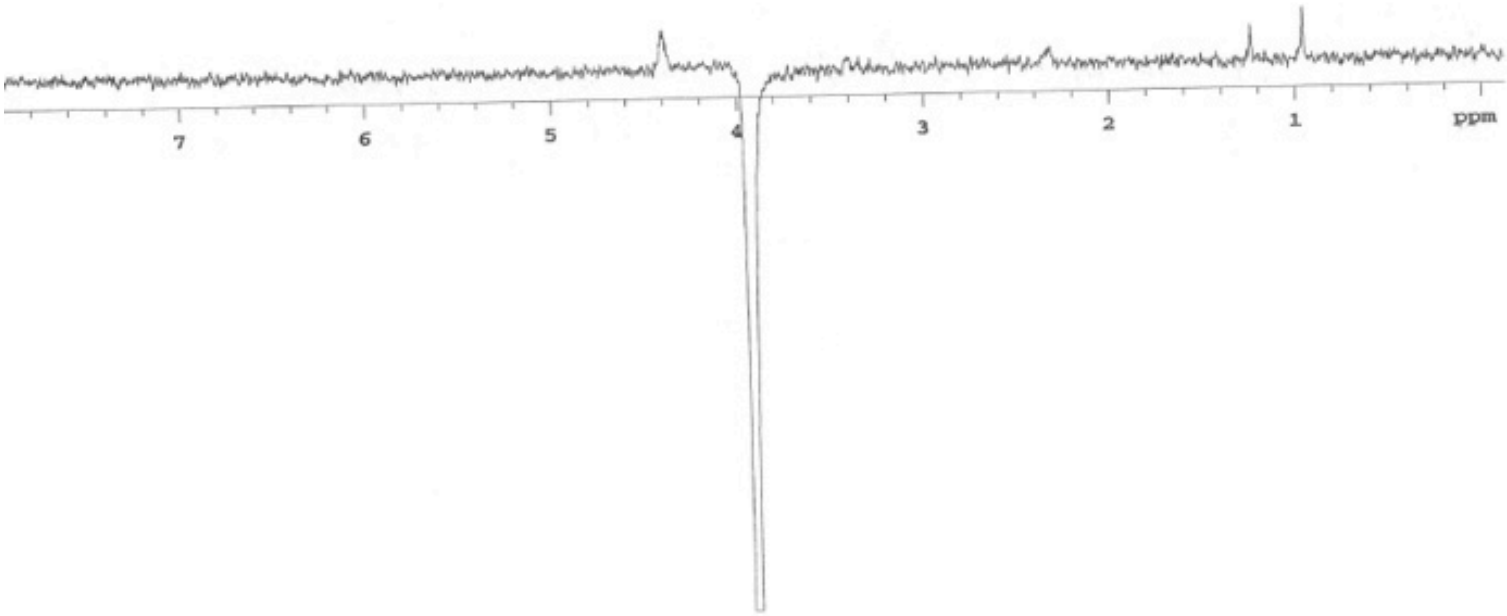
^{13}C NMR, 100 MHz, C_6D_6

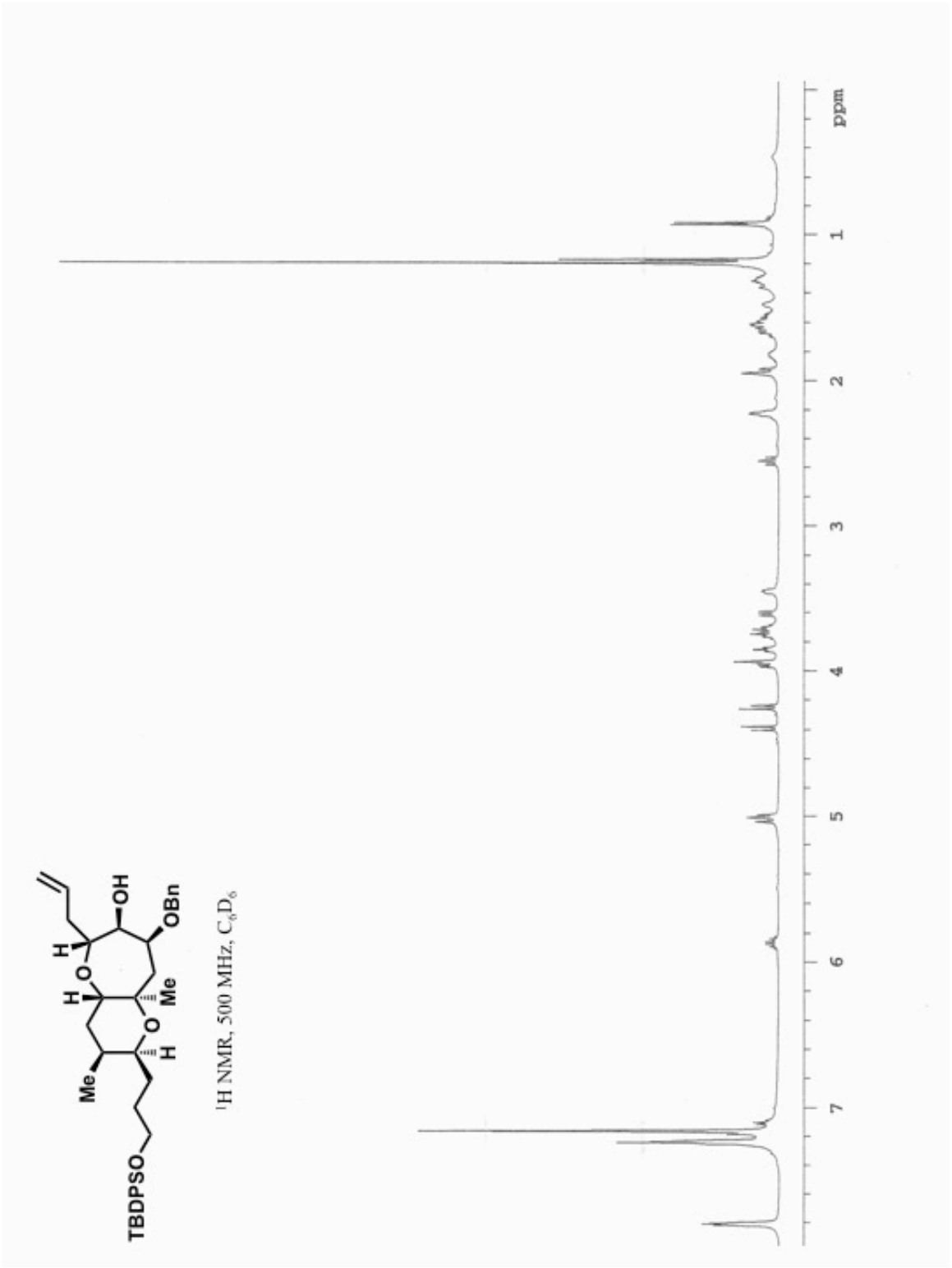


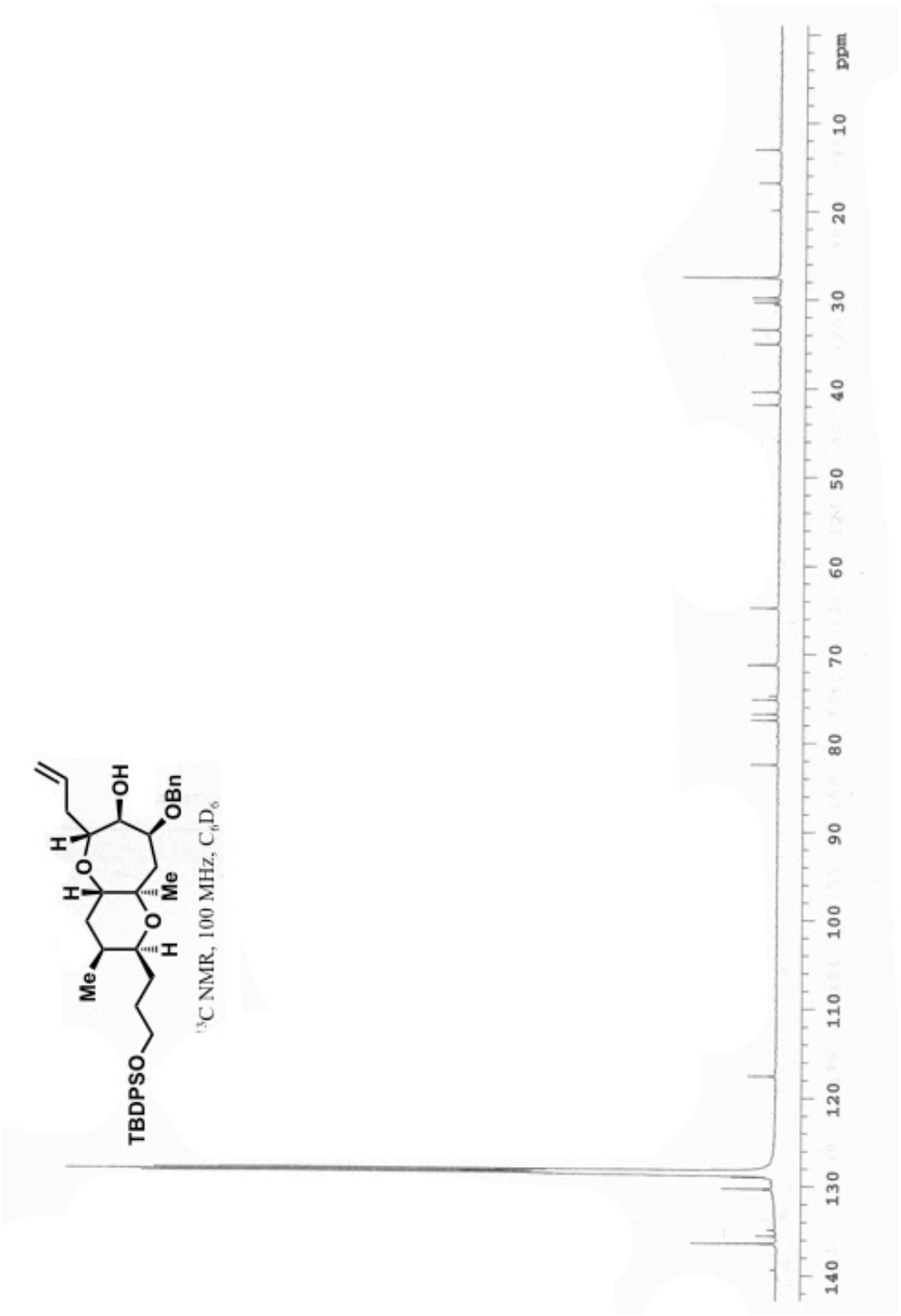
gCOSY NMR, 500 MHz, C_6D_6

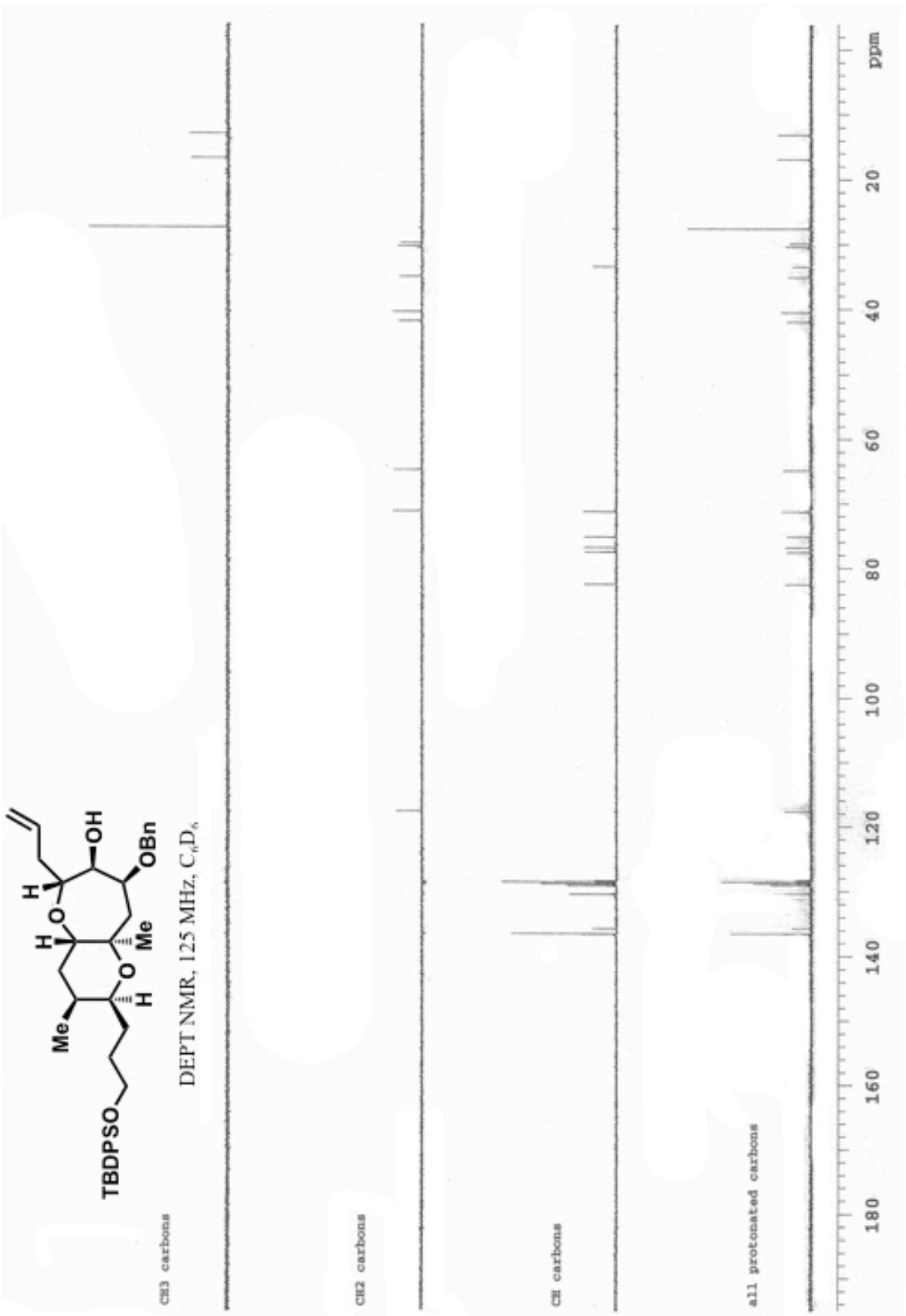


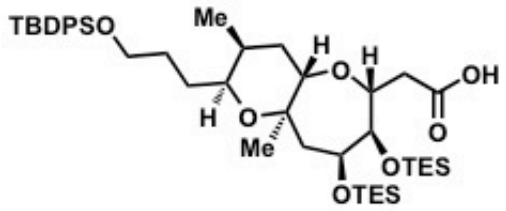
nOe difference, 500 MHz, C_6D_6



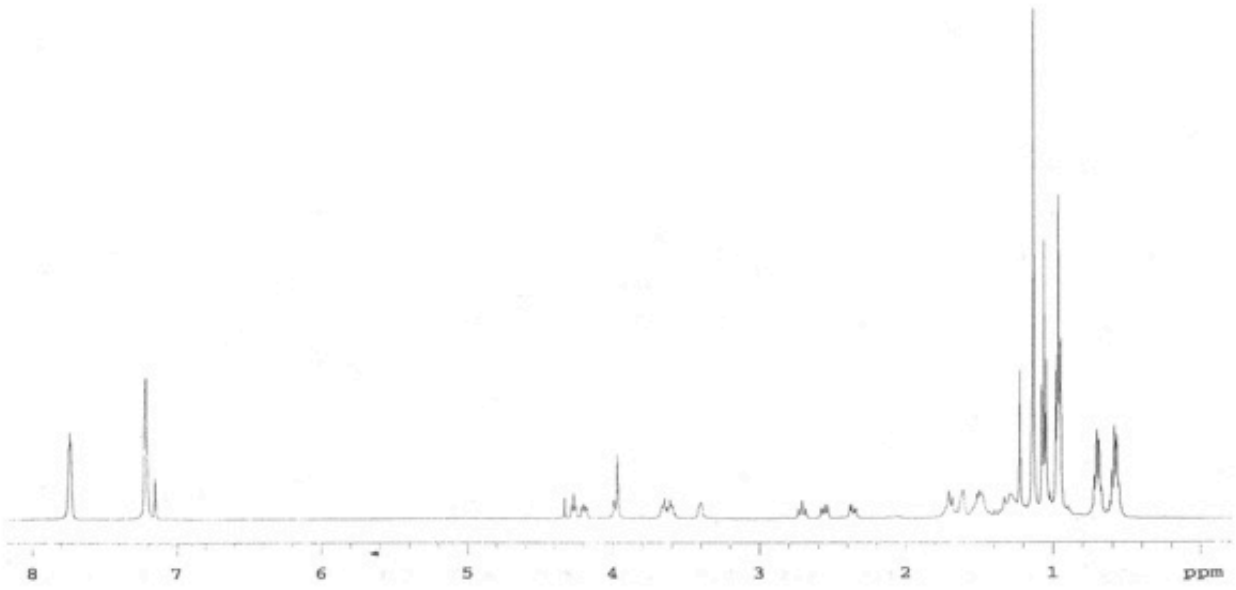

TBDPSO
Me
H
O
H
O
H
Me
OH
OBn
^{1}H NMR, 500 MHz, C_6D_6
7
6
5
4
3
2
1
ppm

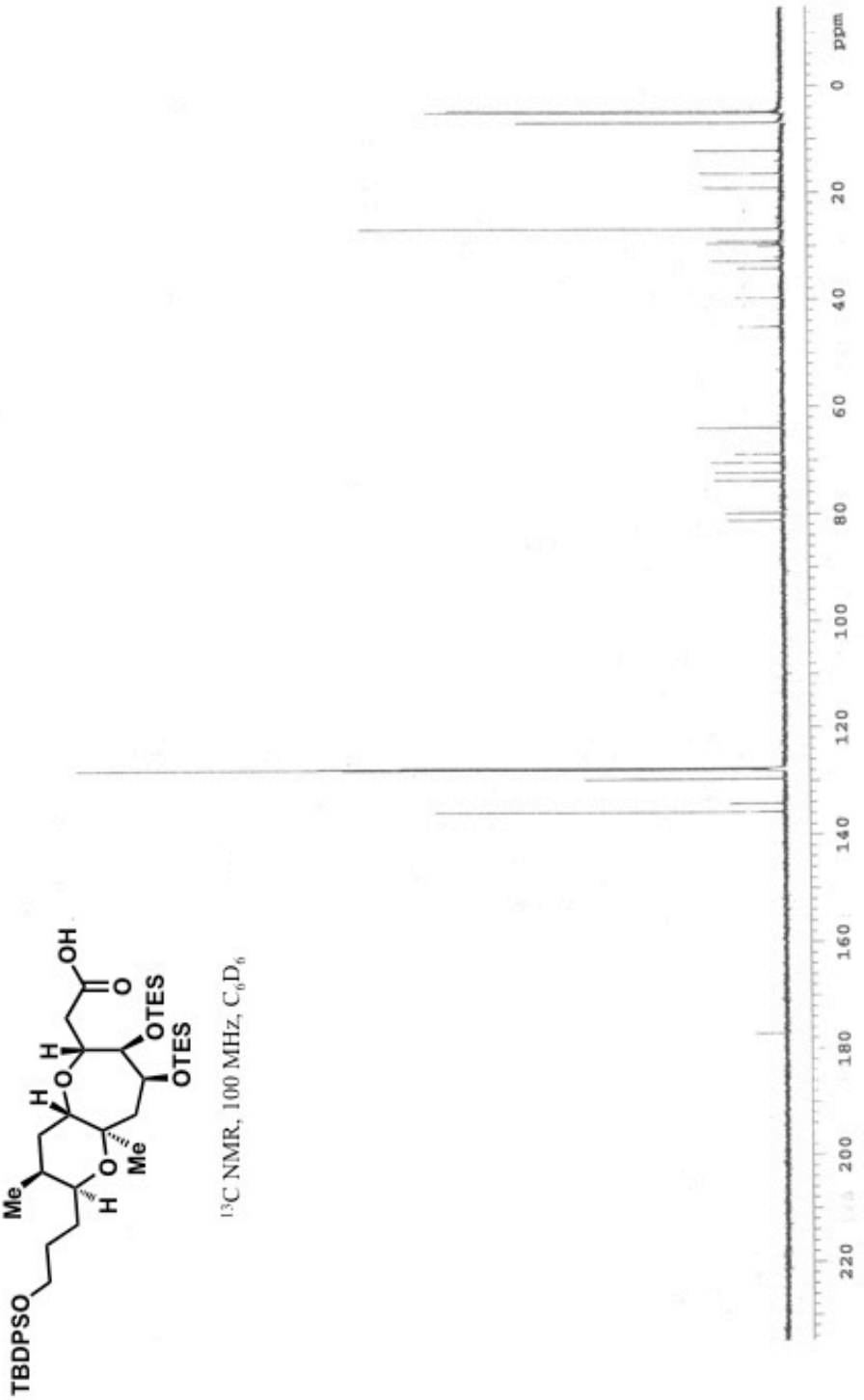

TBDPSO
Me
H
O
H
OH
OBn
Me
O
H
^{13}C NMR, 100 MHz, C_6D_6
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


TBDPSO
Me
H
O
H
O
H
Me
OBn
OH
DEPT NMR, 125 MHz, C_6D_6
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
180
160
140
120
100
80
60
40
20
ppm



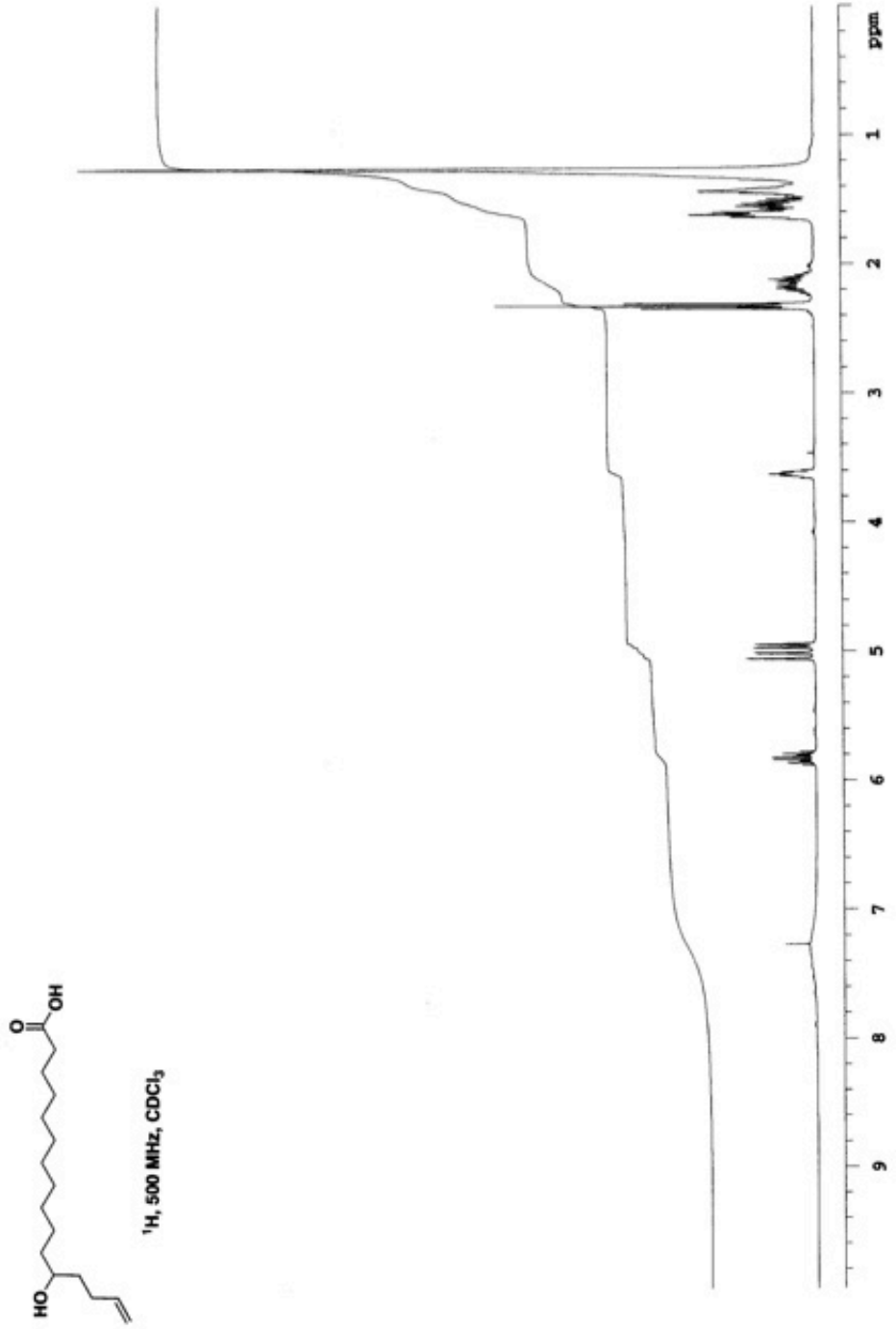
^{1}H NMR, 500 MHz, C_6D_6

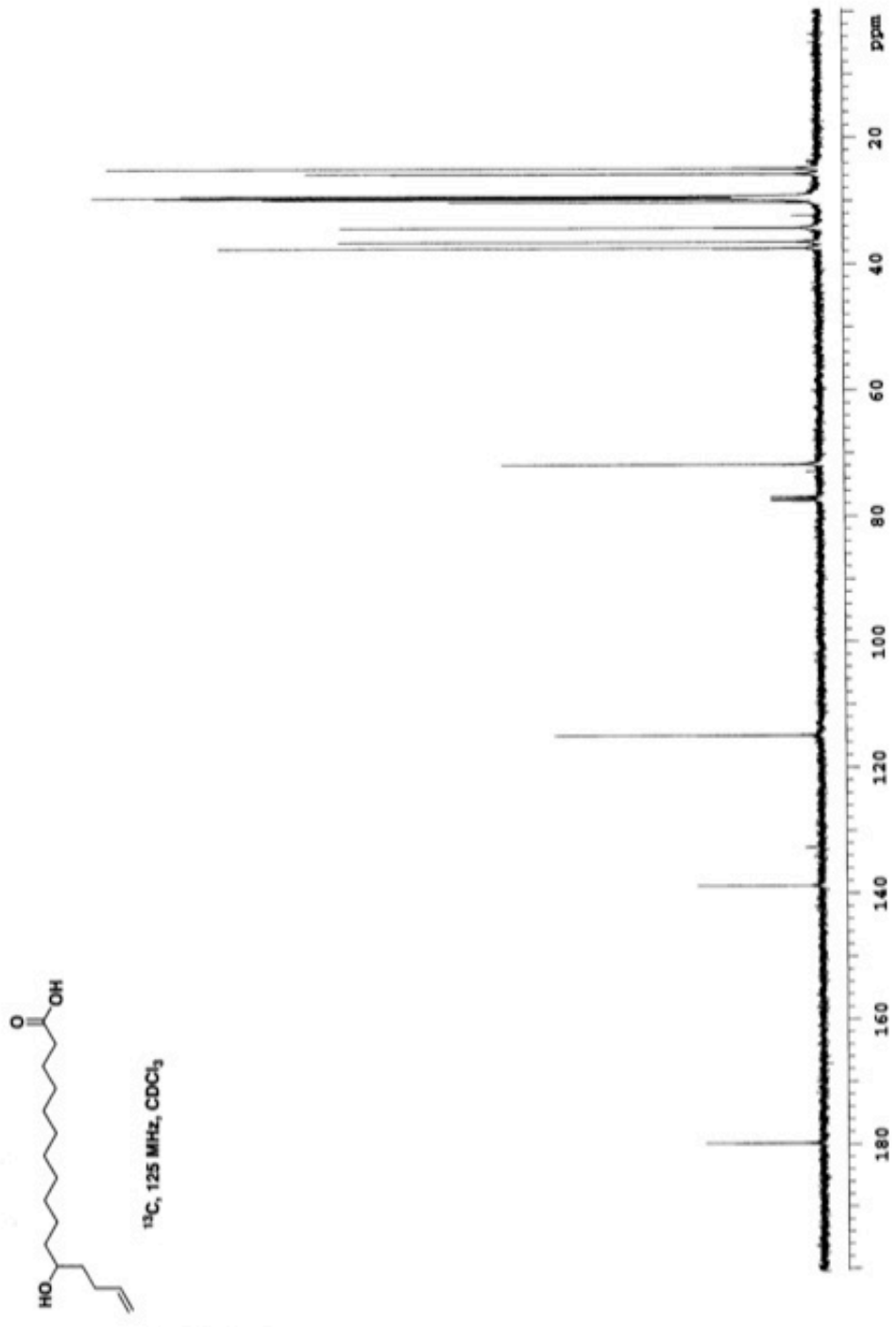


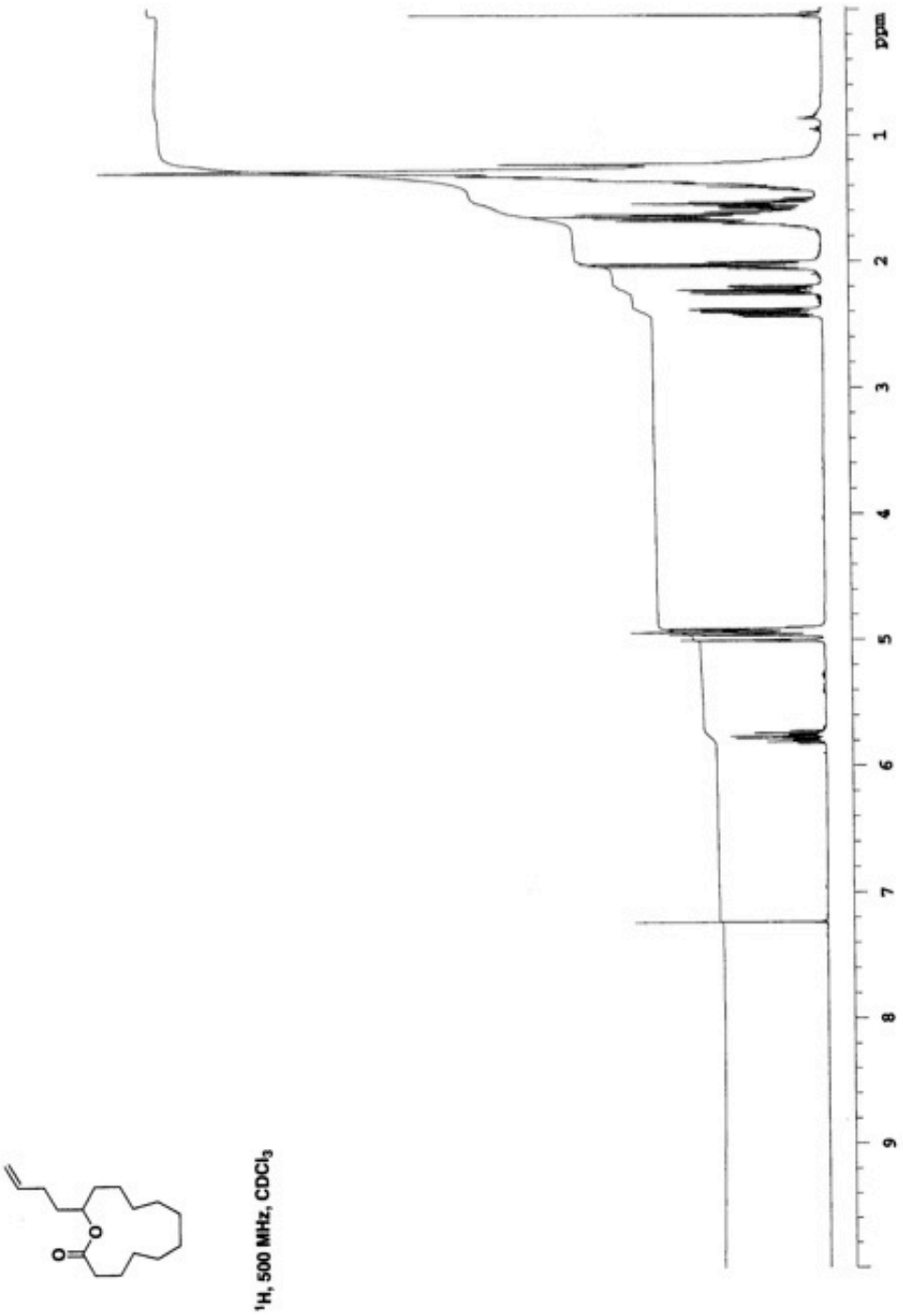


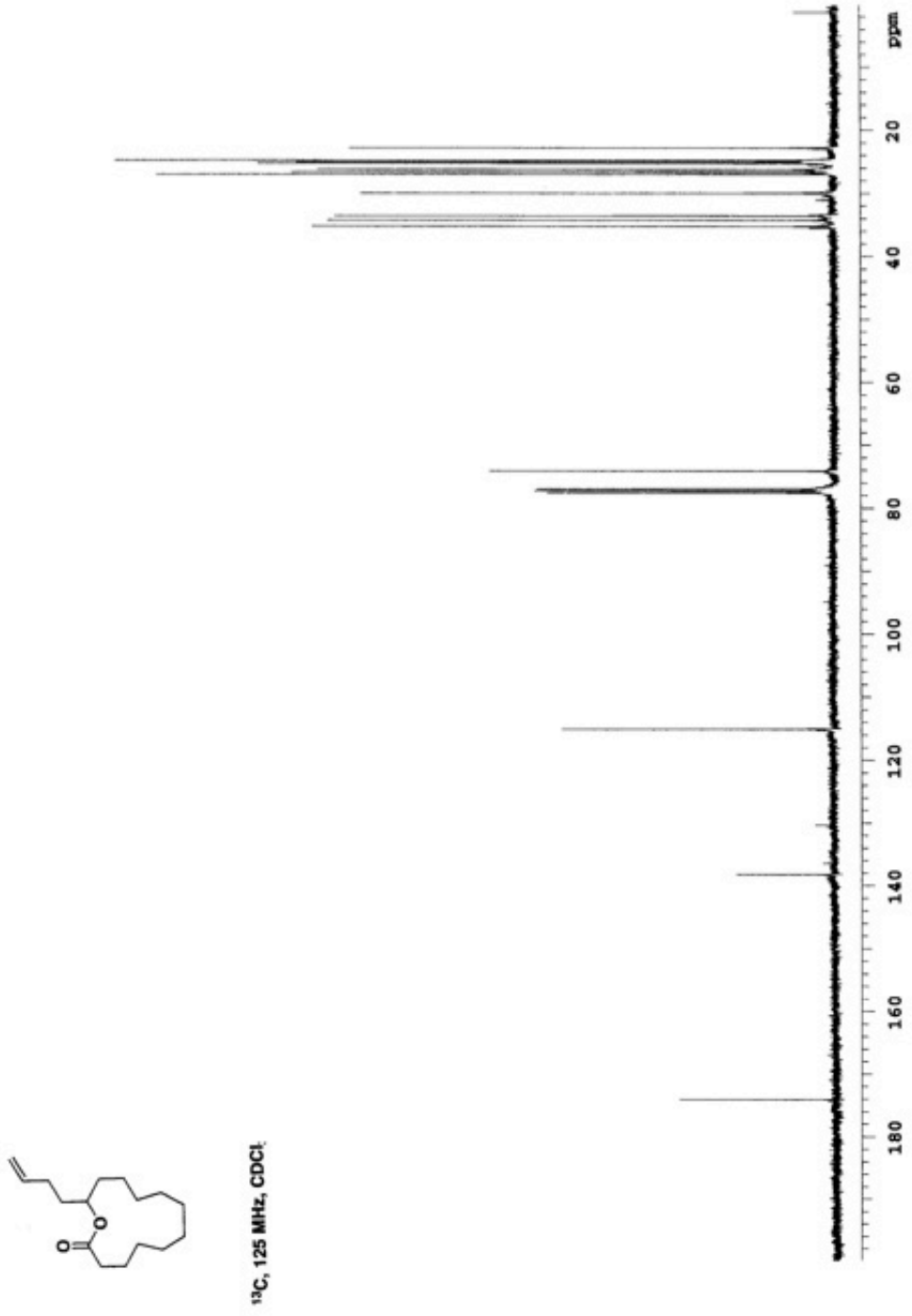
^{13}C NMR, 100 MHz, C_6D_6

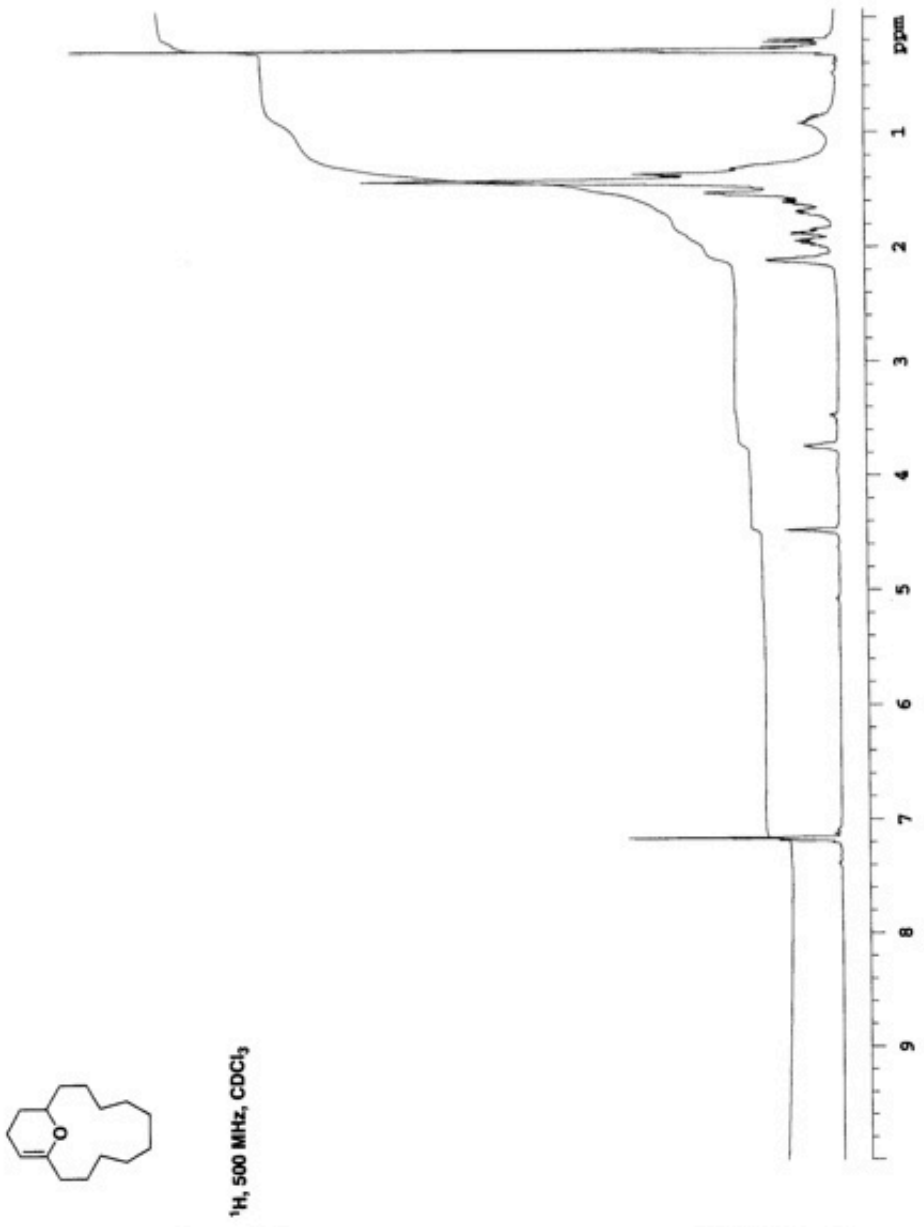
APPENDIX B: ^{1}H, AND ^{13}C NMR SPECTRA CHAPTER 2

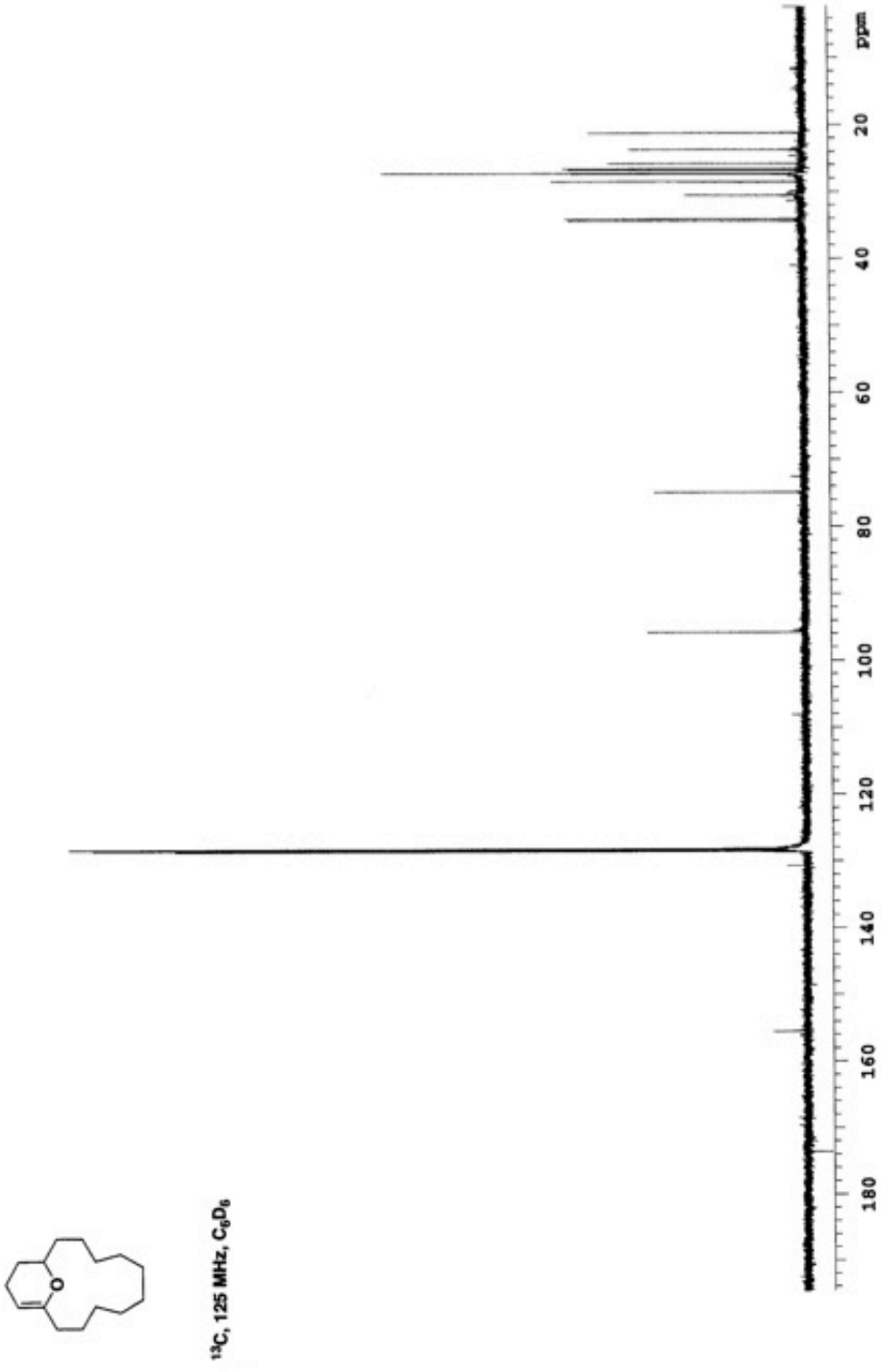

O
OH
HO
^{1}H, 500 MHz, $CDCl_3$
1
2
3
4
5
6
7
8
9
ppm

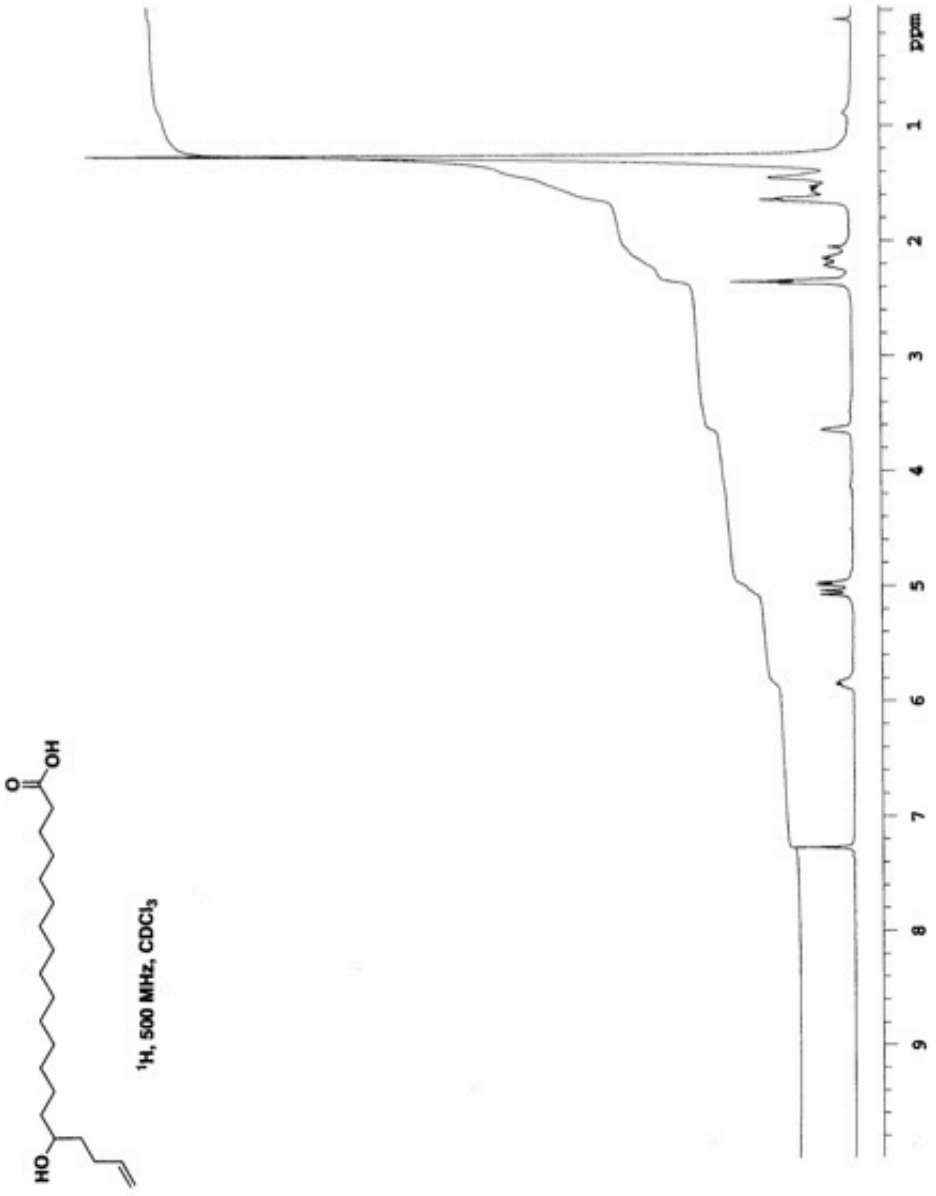

O
OH
HO
^{13}C, 125 MHz, $CDCl_3$
ppm
20
40
60
80
100
120
140
160
180

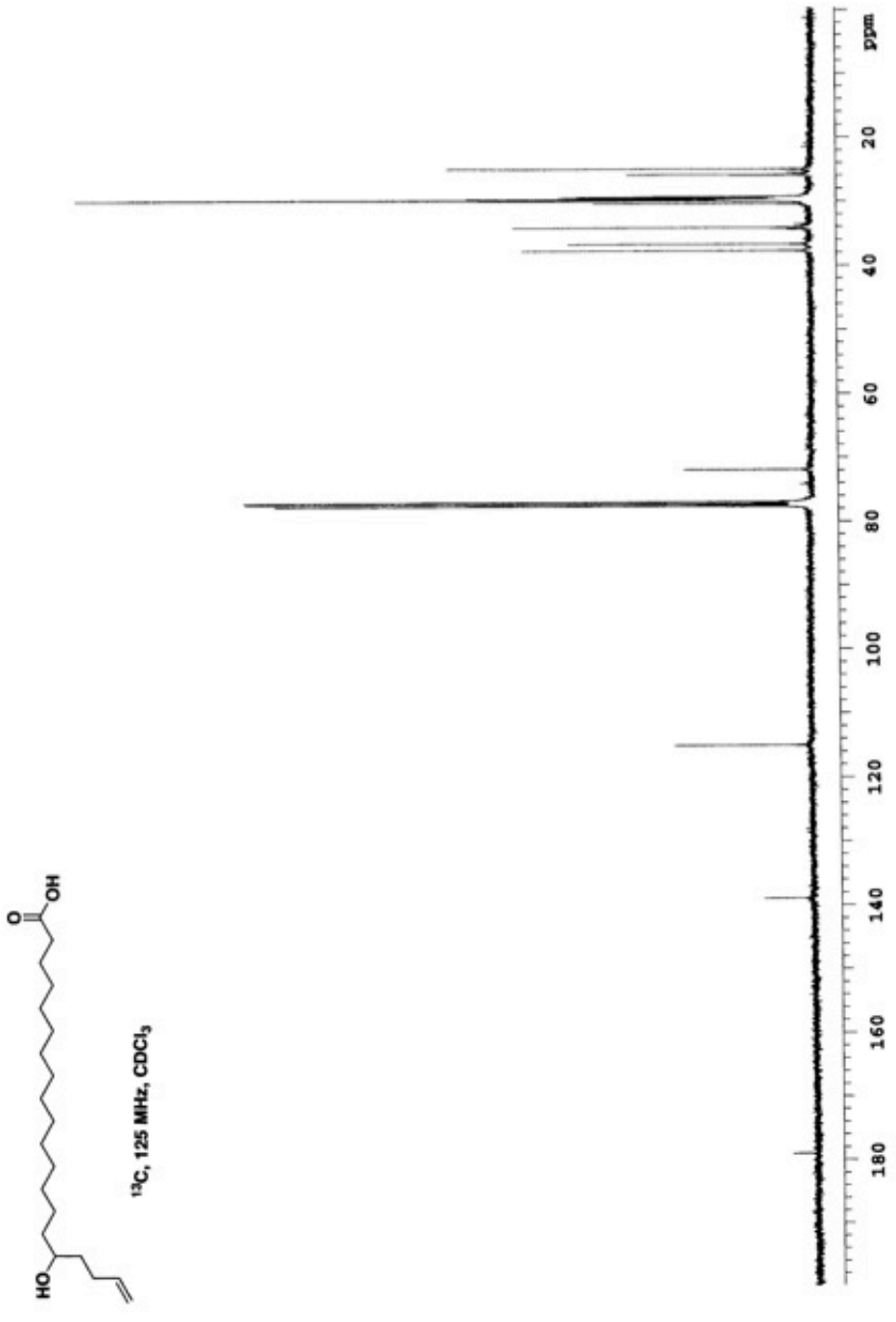

ppm
1
2
3
4
5
6
7
8
9
O
O
^{1}H, 500 MHz, $CDCl_3$

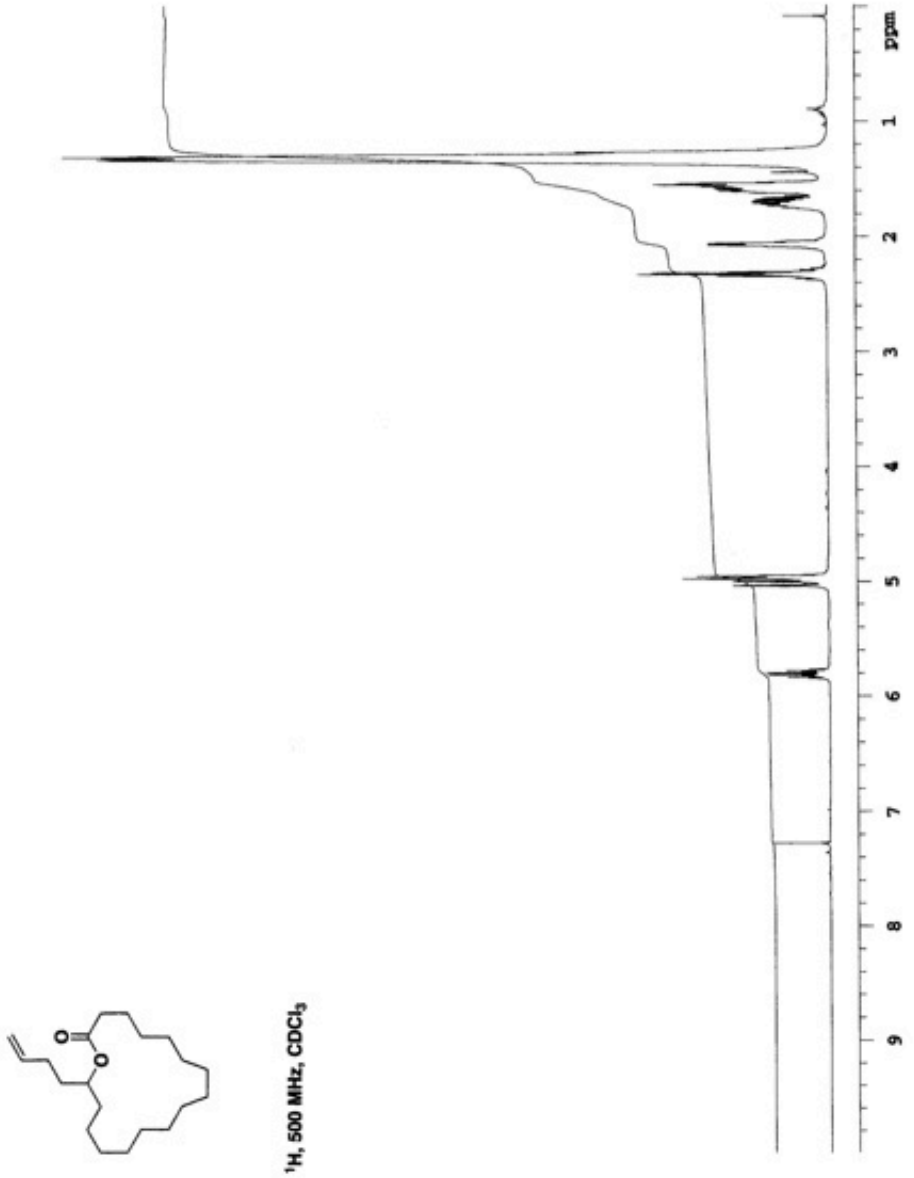

O
O
^{13}C, 125 MHz, CDCl
180
160
140
120
100
80
60
40
20
ppm

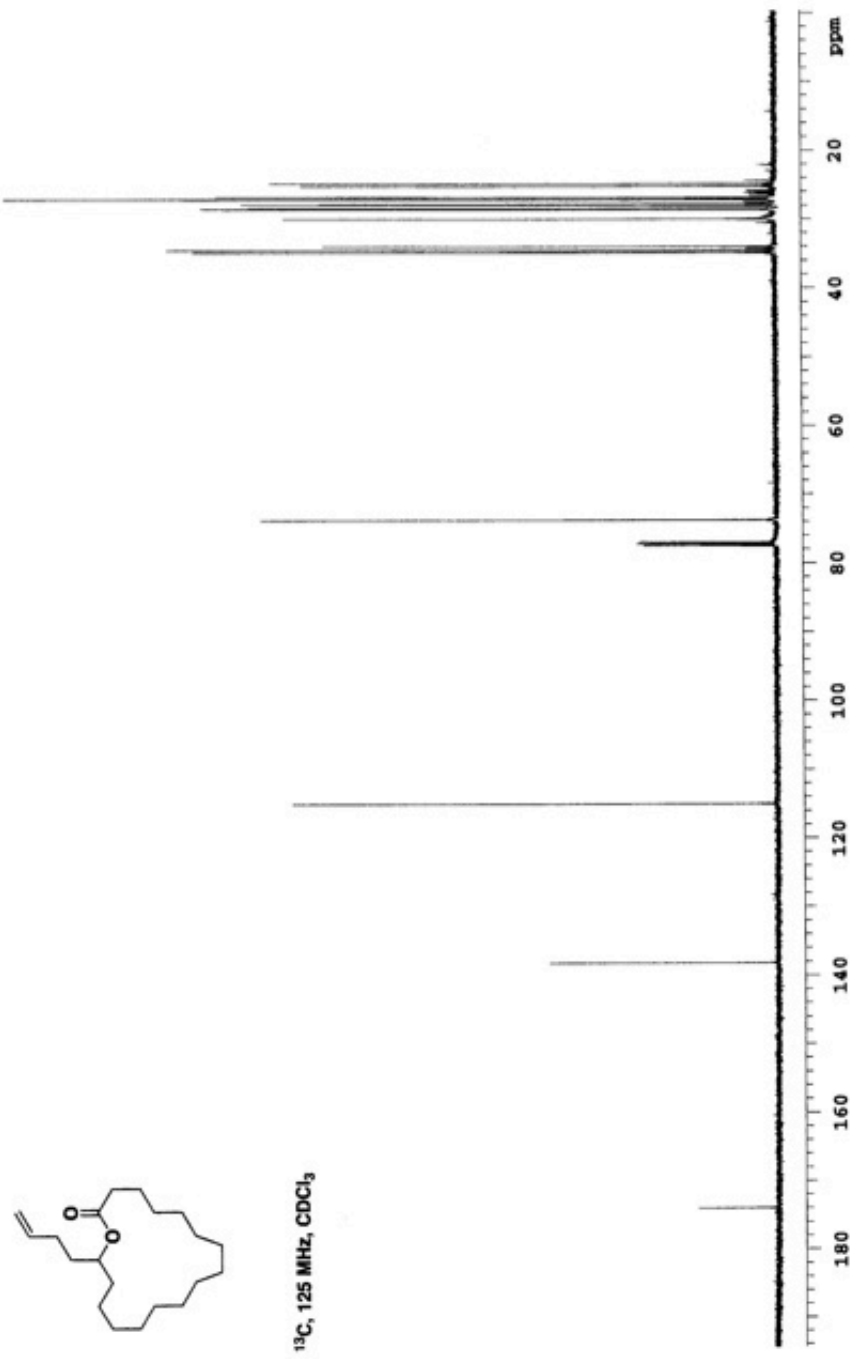

O
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9

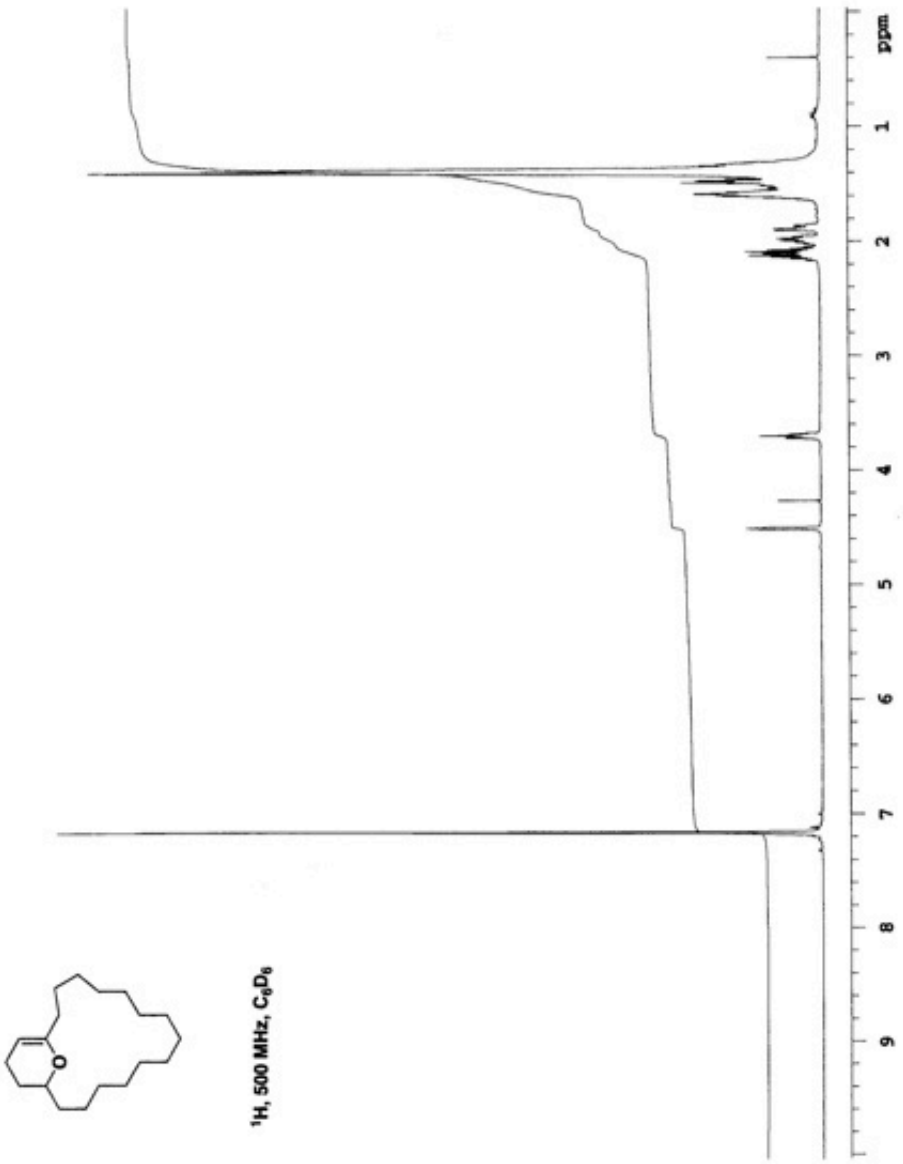

O
^{13}C, 125 MHz, C_6D_6
ppm
20
40
60
80
100
120
140
160
180

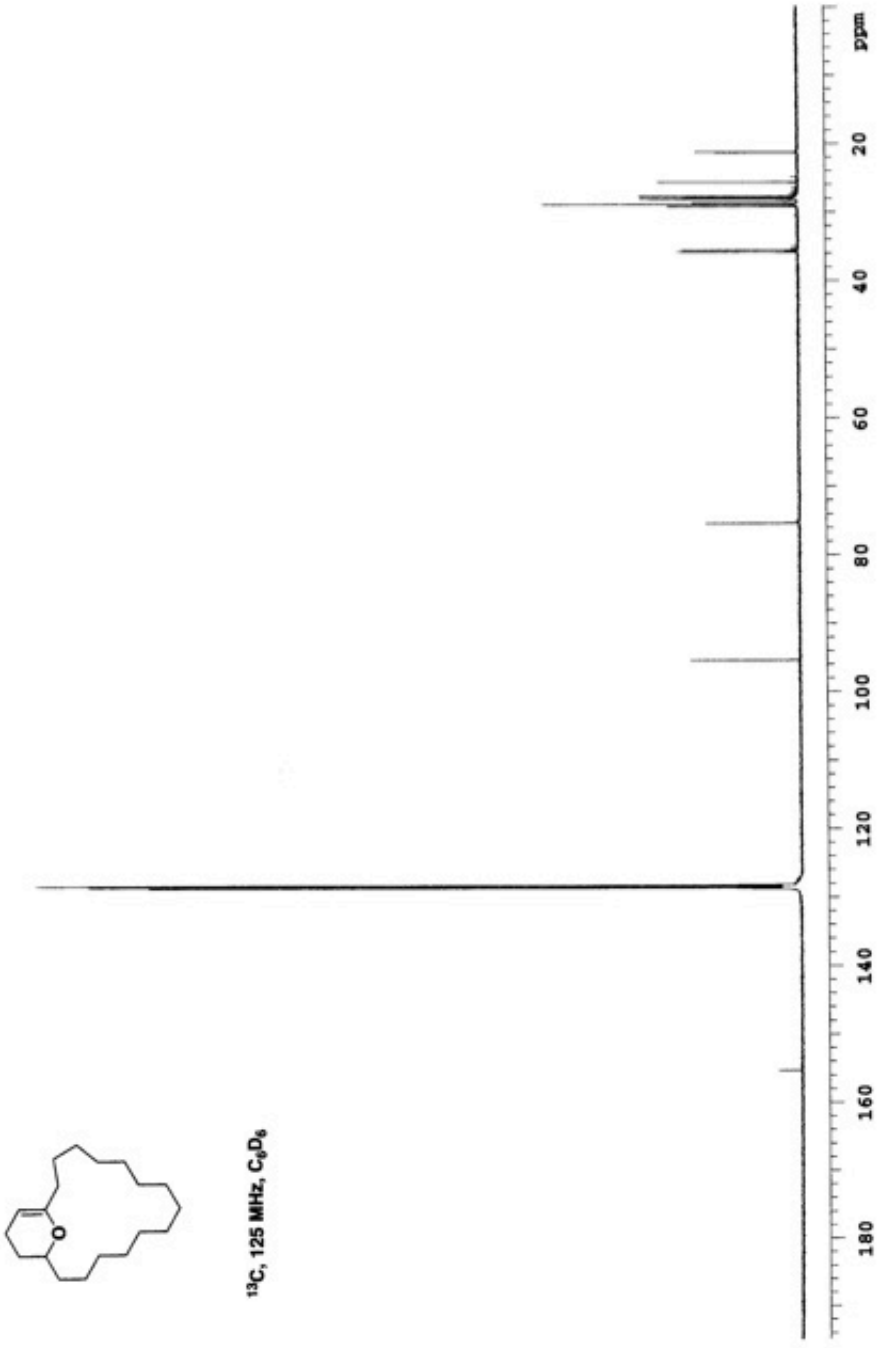

HO
O
OH
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9

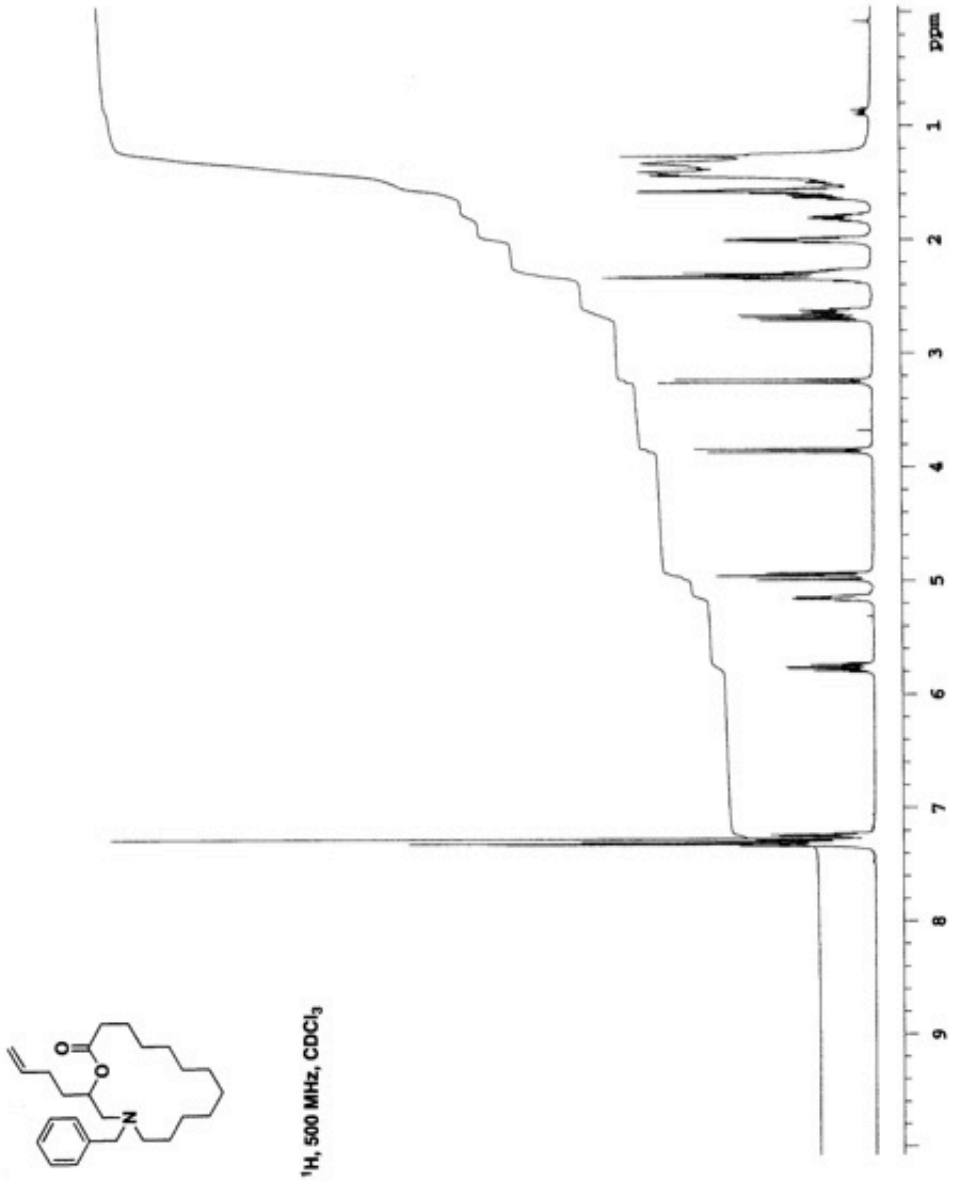

O
OH
HO
^{13}C, 125 MHz, $CDCl_3$
ppm
20
40
60
80
100
120
140
160
180

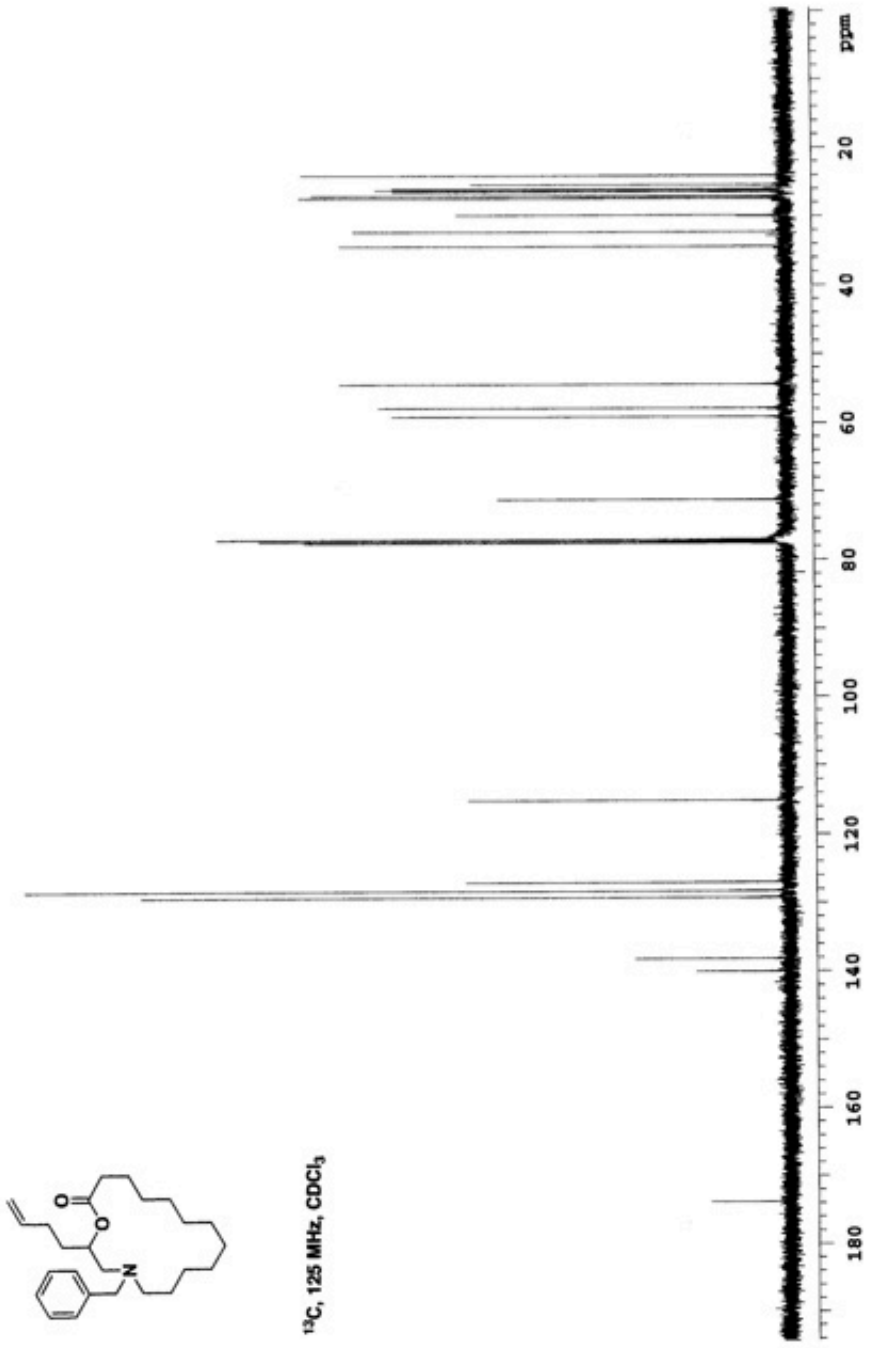

O
O
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9

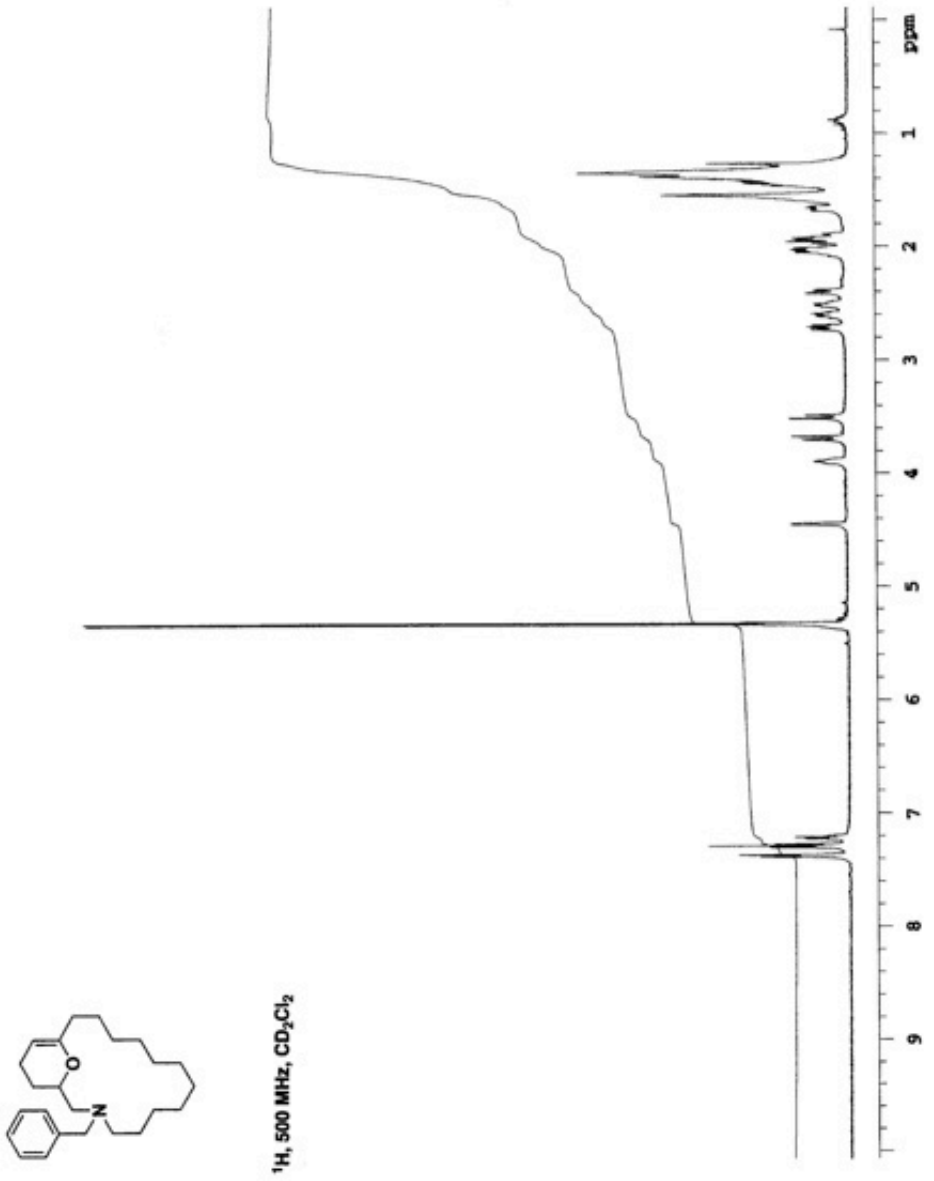

O
O
^{13}C, 125 MHz, $CDCl_3$
180
160
140
120
100
80
60
40
20
ppm

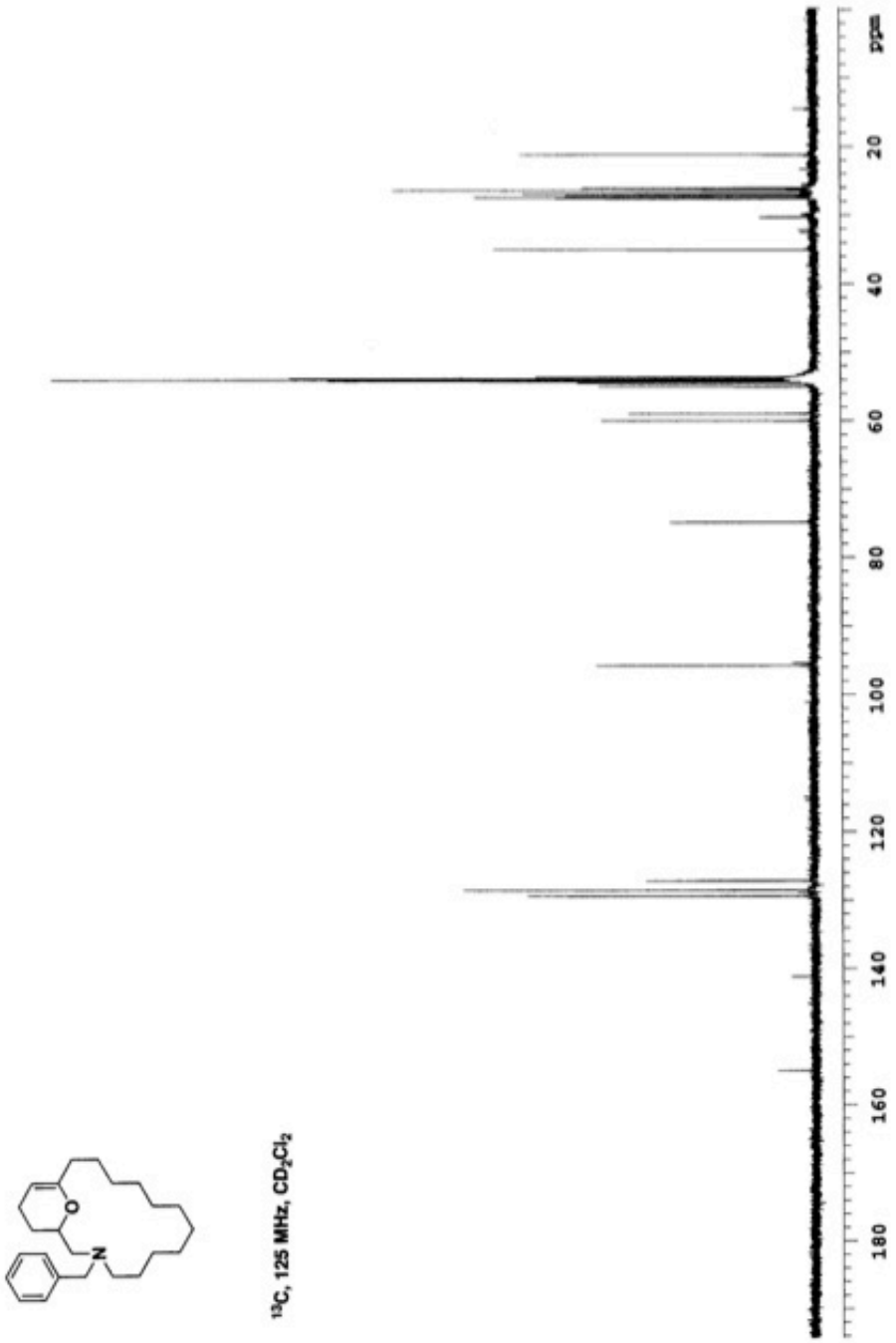

O
^{1}H, 500 MHz, C_6D_6
ppm
1
2
3
4
5
6
7
8
9

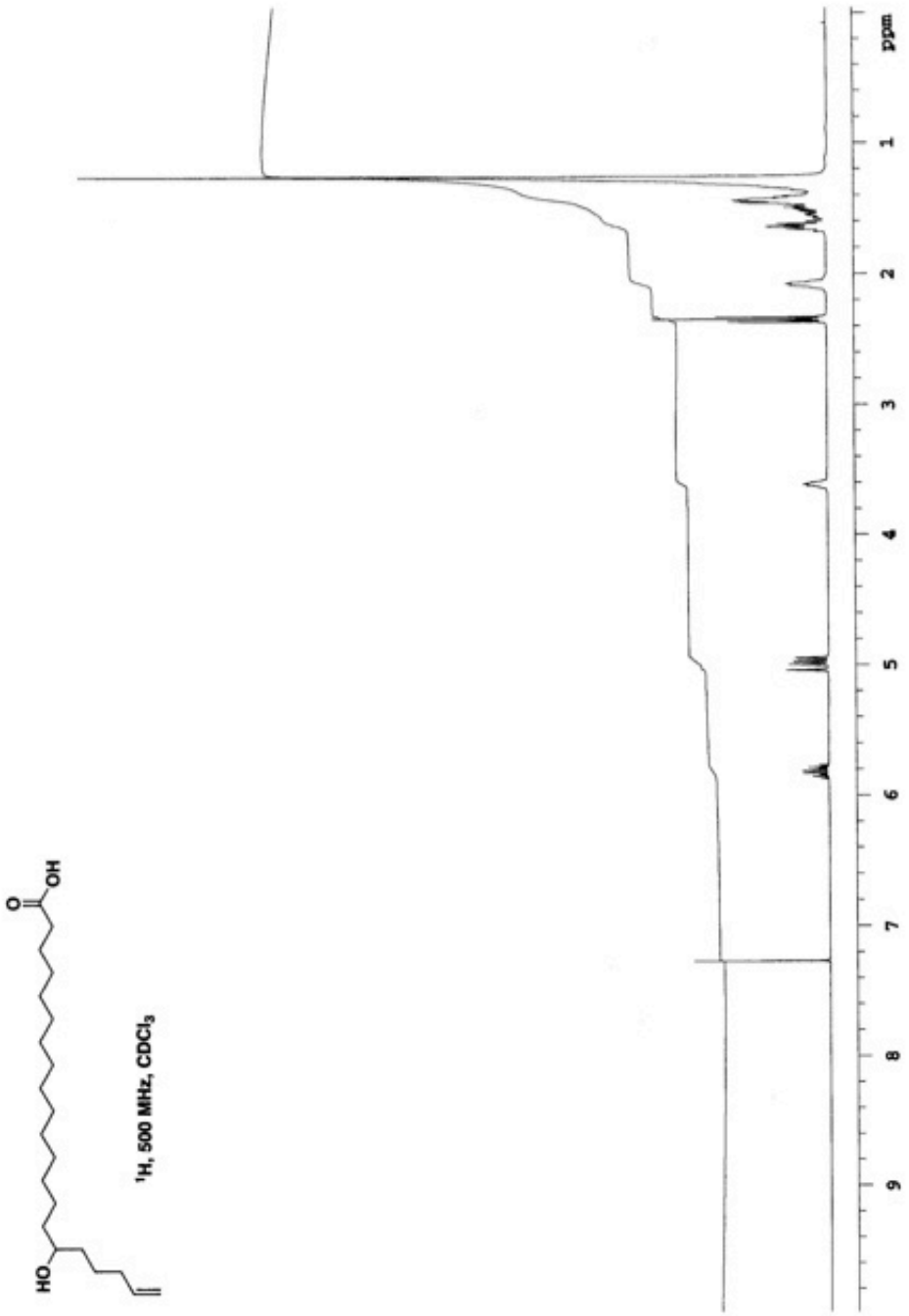

^{13}C, 125 MHz, C_6D_6
O
180
160
140
120
100
80
60
40
20
ppm

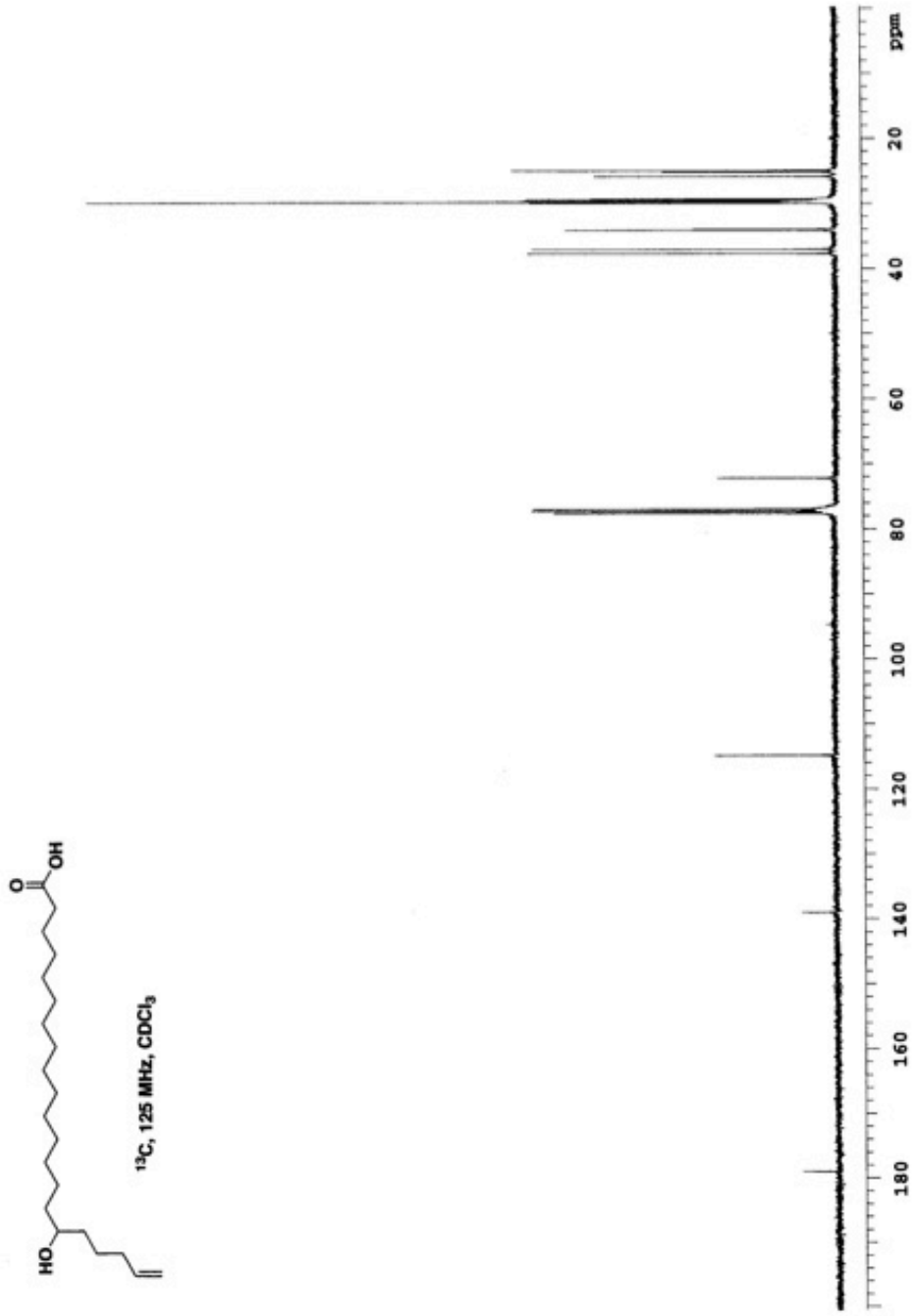

O
O
N
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9

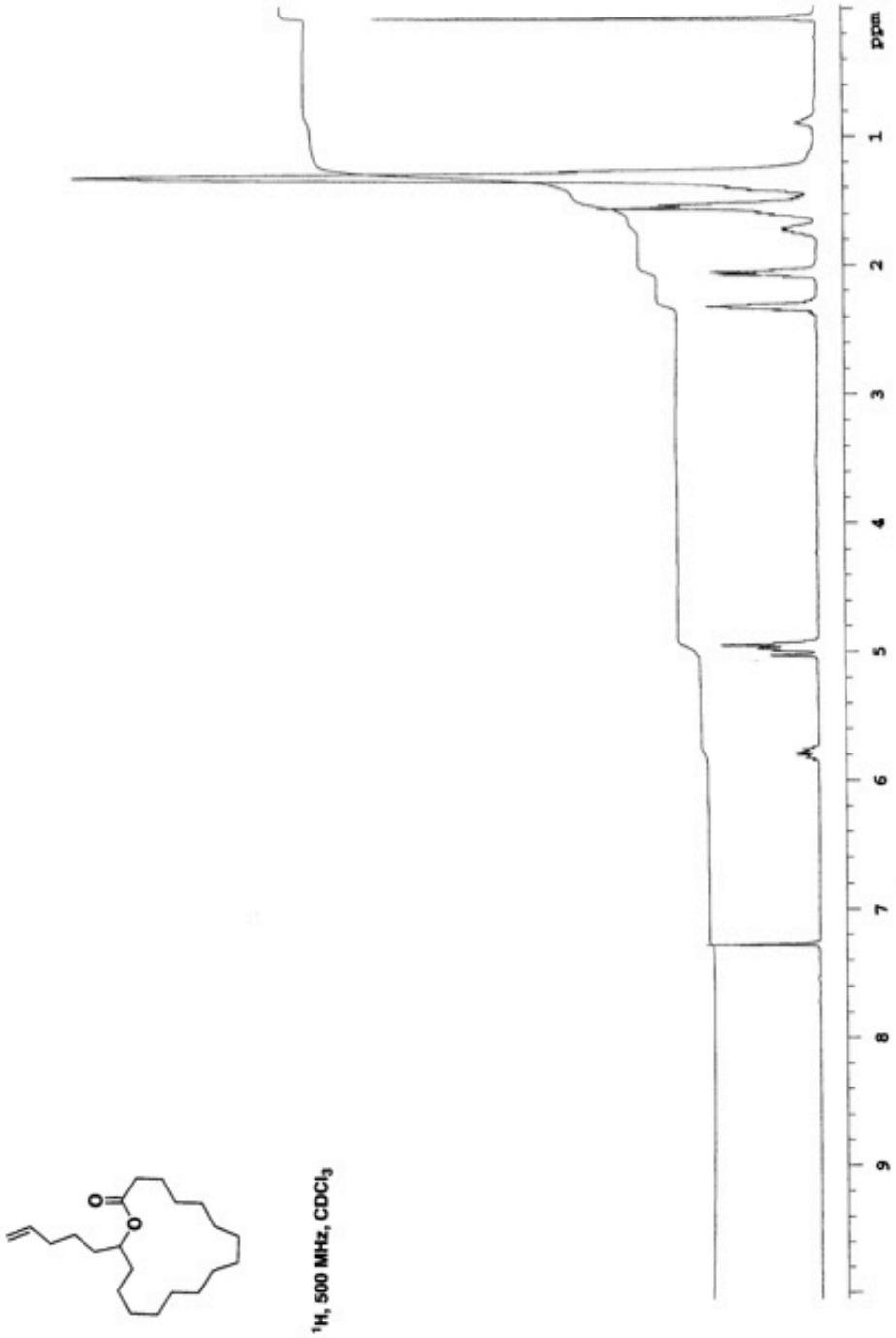

O
O
N
^{13}C, 125 MHz, $CDCl_3$
ppm
20
40
60
80
100
120
140
160
180

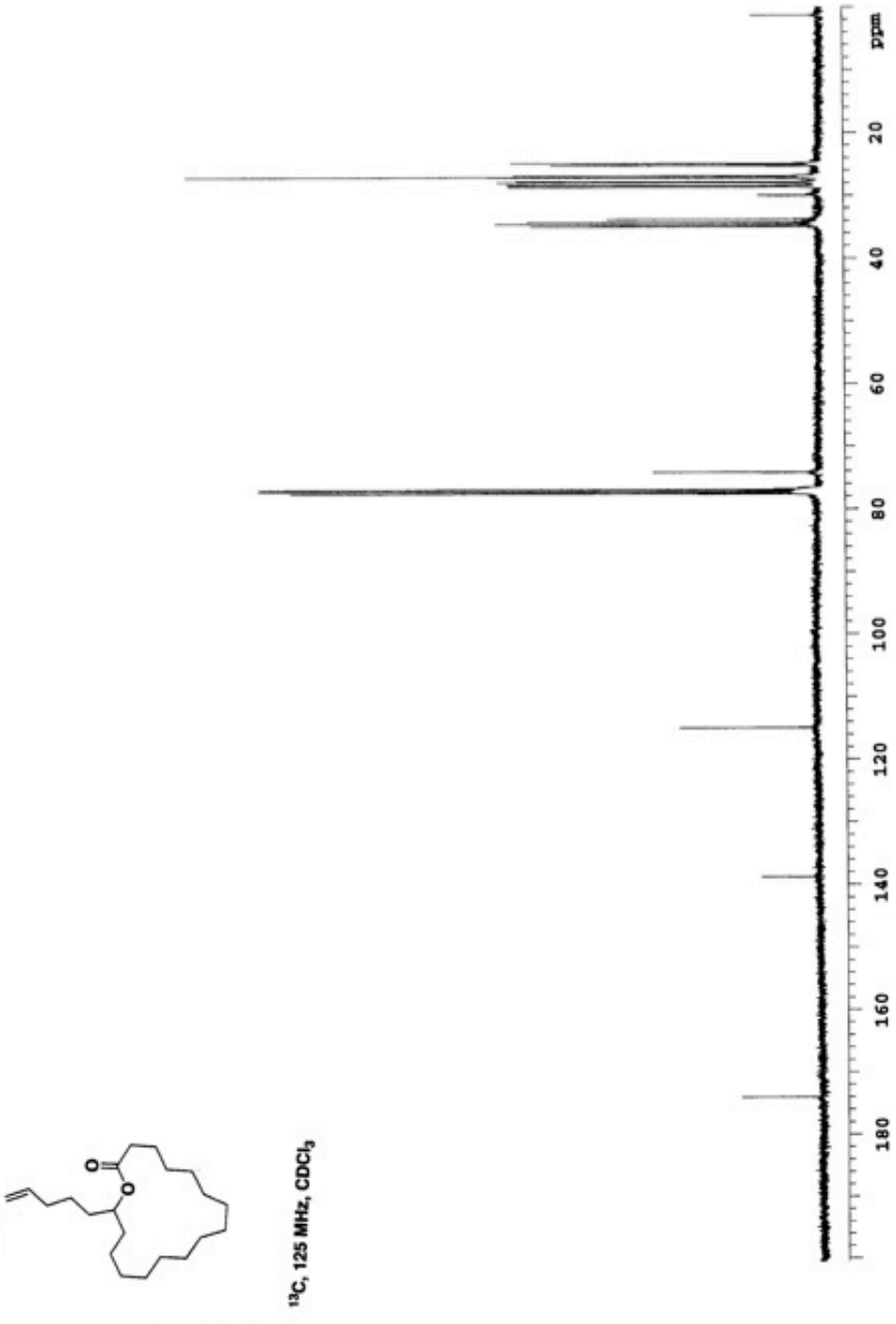

O
N
^{1}H, 500 MHz, CD_2Cl_2
9
8
7
6
5
4
3
2
1
ppm

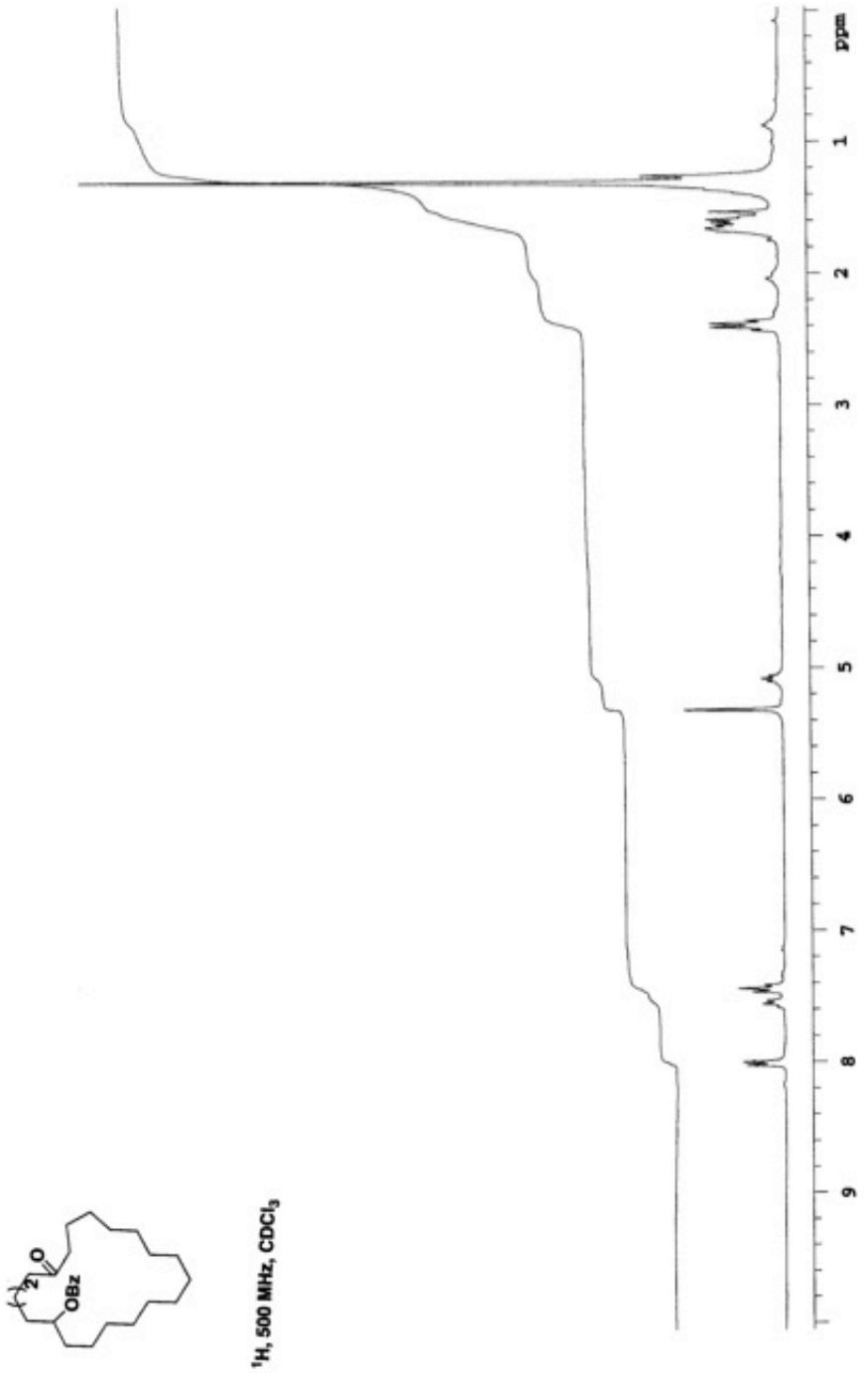

O
N
^{13}C, 125 MHz, CD_2Cl_2
ppm
20
40
60
80
100
120
140
160
180

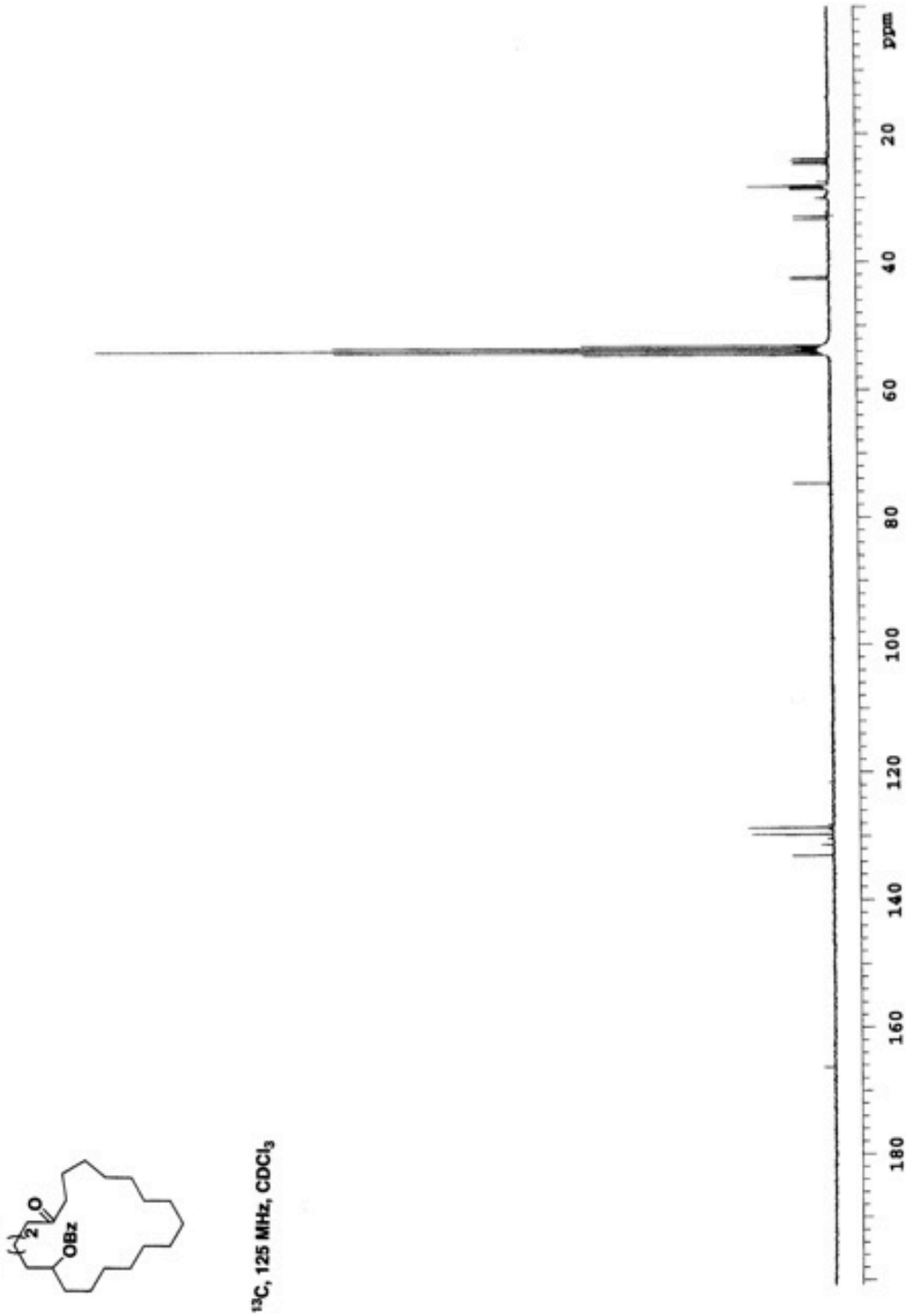

O
OH
HO
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9

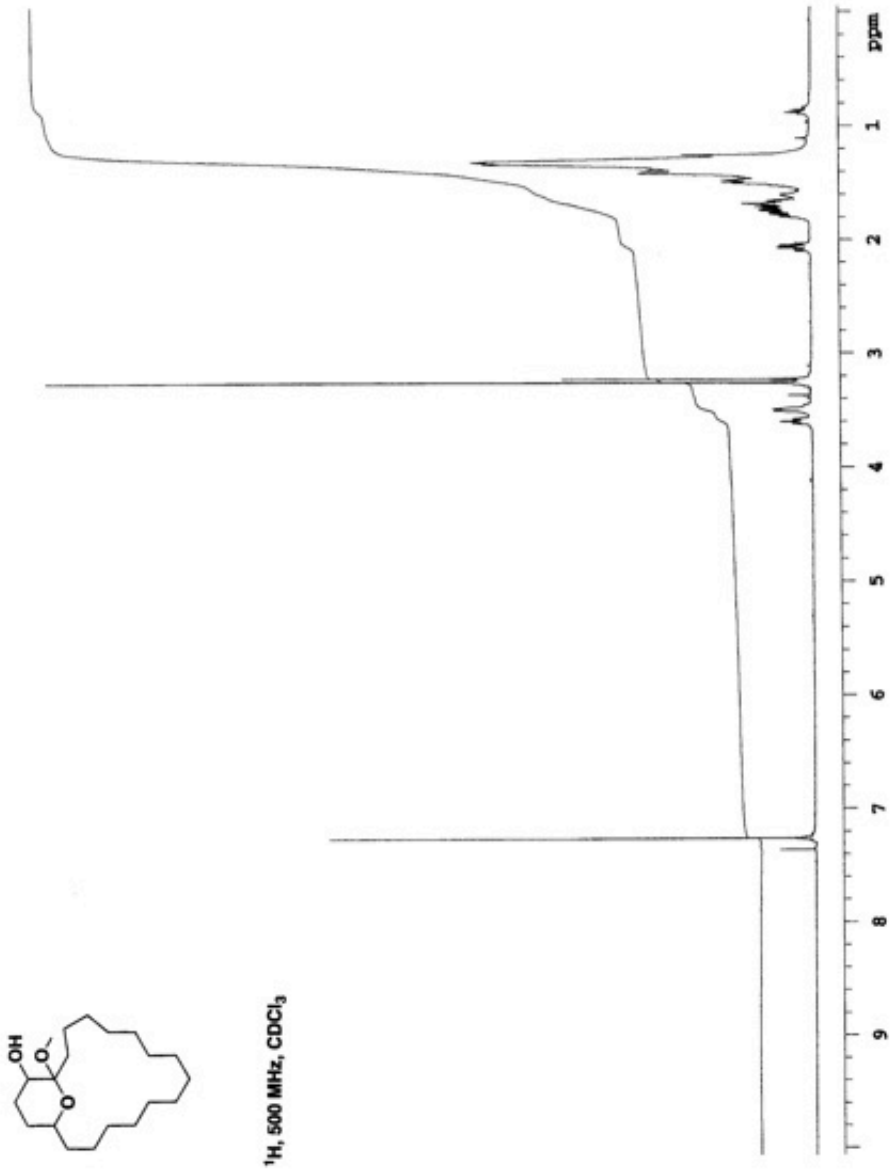

O
OH
HO
^{13}C, 125 MHz, $CDCl_3$
180
160
140
120
100
80
60
40
20
ppm

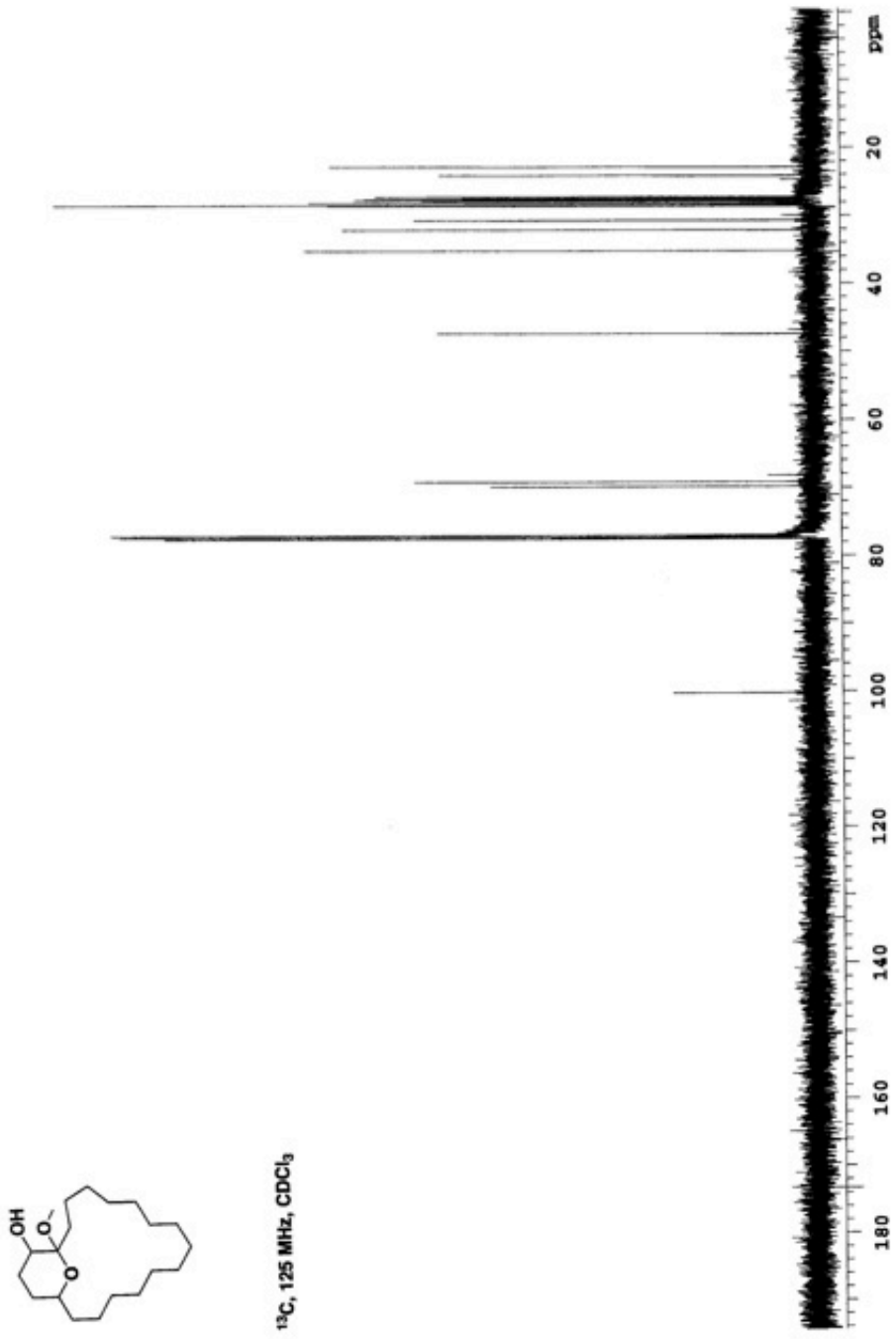

O
O
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9

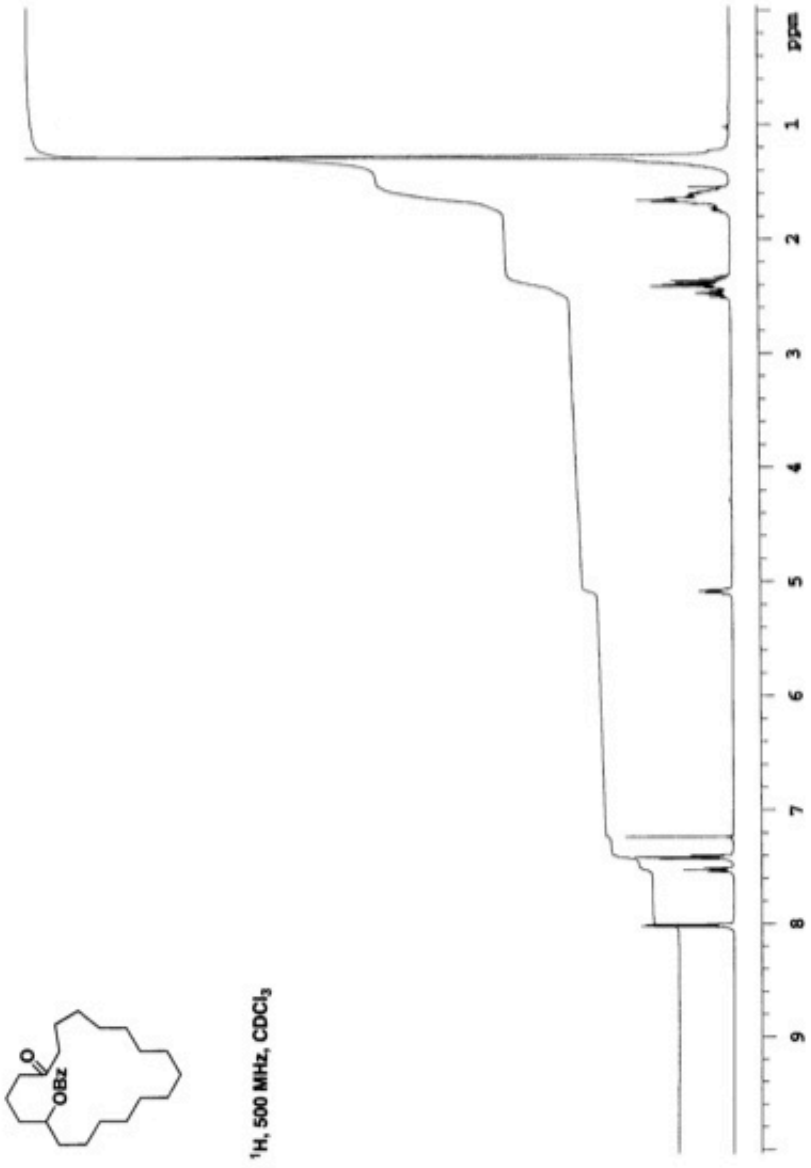

ppm
20
40
60
80
100
120
140
160
180
O
O
^{13}C, 125 MHz, $CDCl_3$

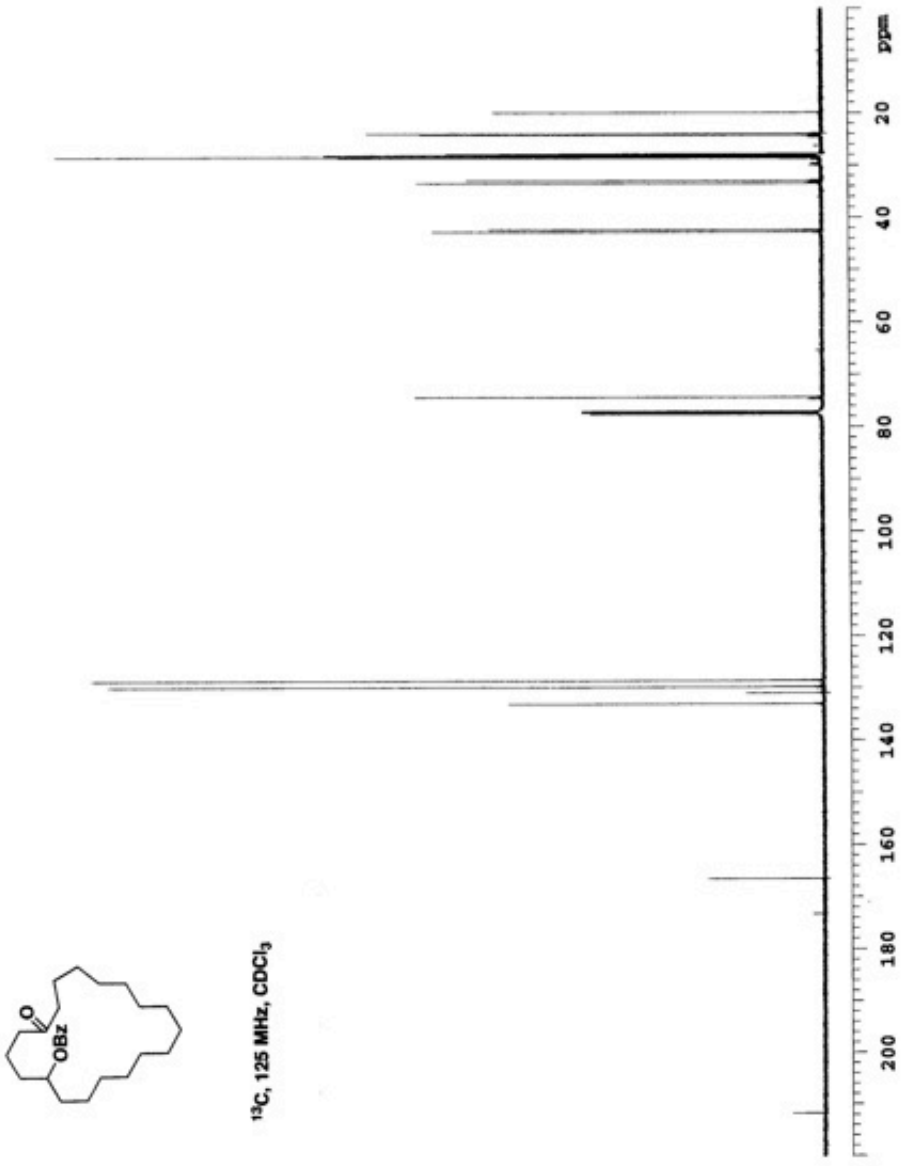

OBz
O
2
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9

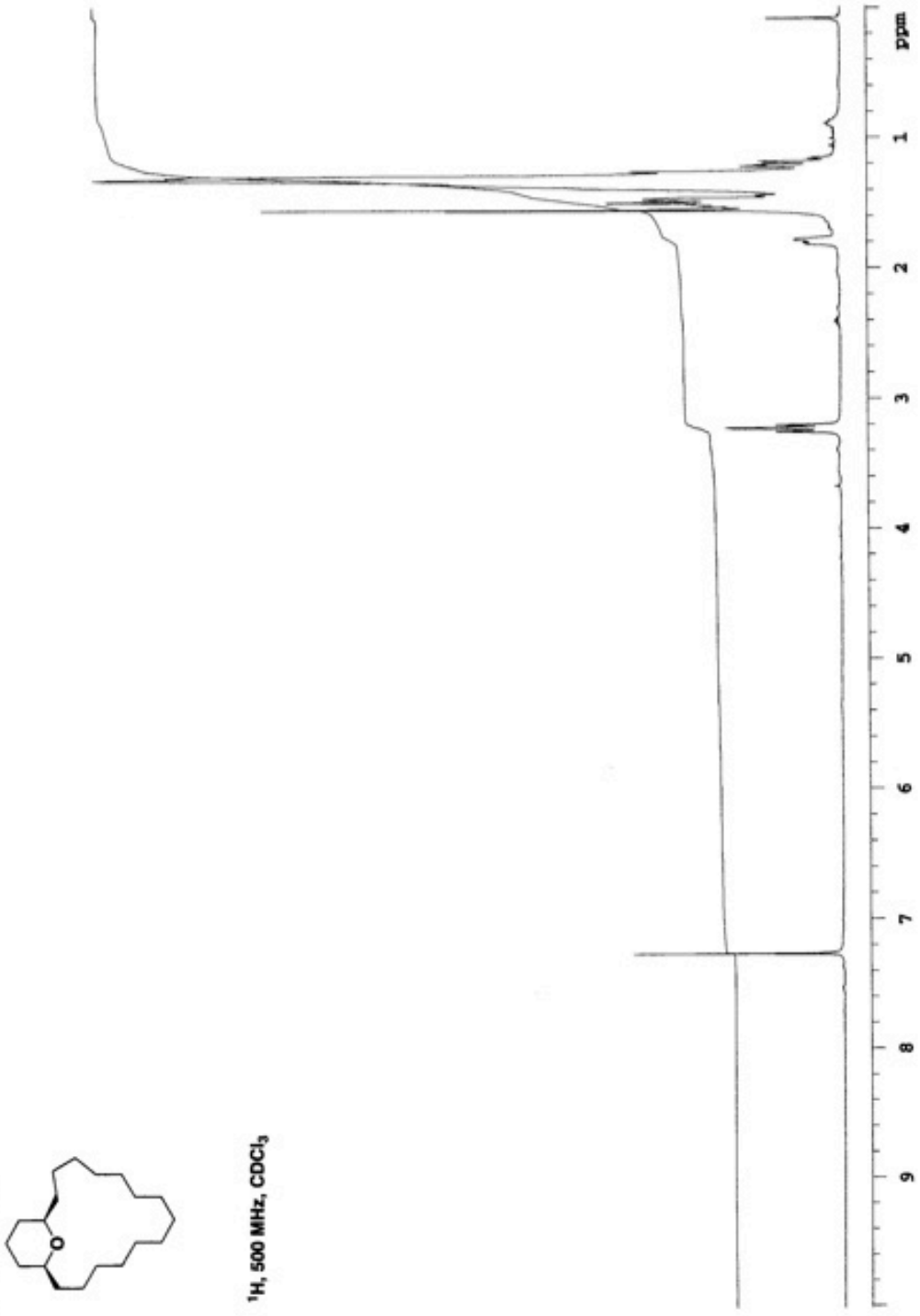

OBz
O
2
^{13}C, 125 MHz, CDCl$_3$
180
160
140
120
100
80
60
40
20
ppm

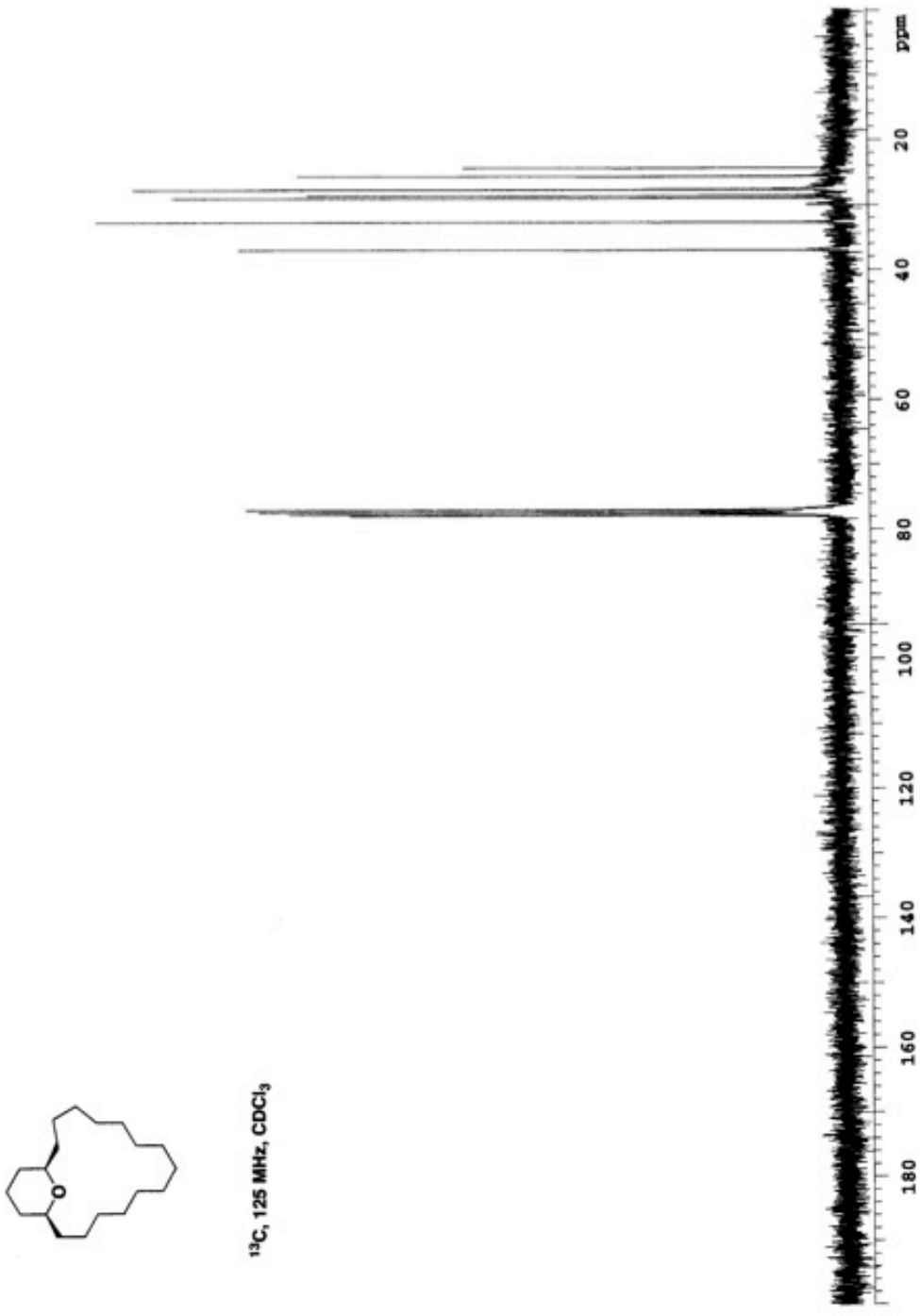

OH
O
O
^{1}H, 500 MHz, CDCl$_3$
ppm
1
2
3
4
5
6
7
8
9

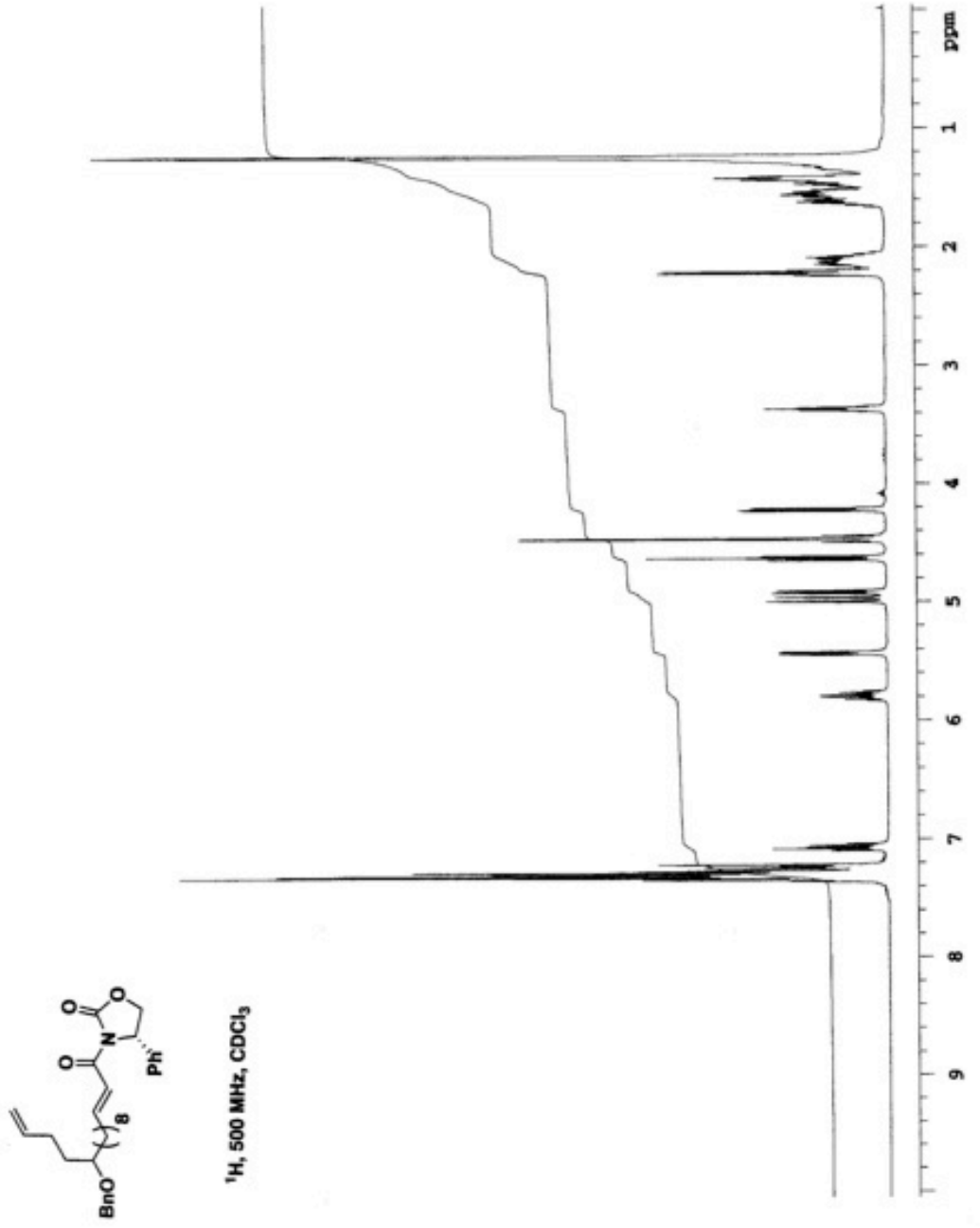

OH
O
O
^{13}C, 125 MHz, $CDCl_3$
ppm
20
40
60
80
100
120
140
160
180

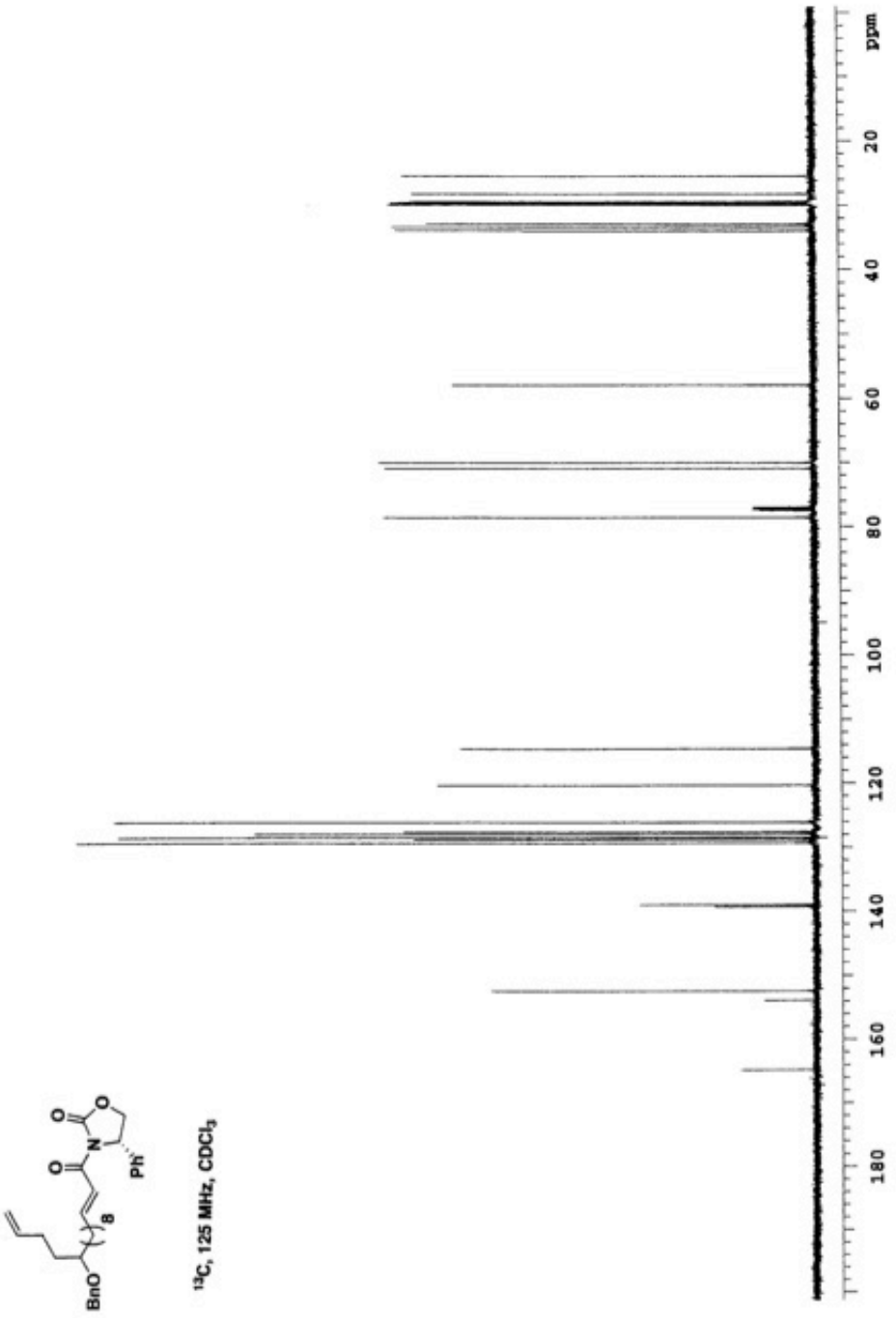

O
OBz
^{1}H, 500 MHz, $CDCl_3$
9
8
7
6
5
4
3
2
1
ppm

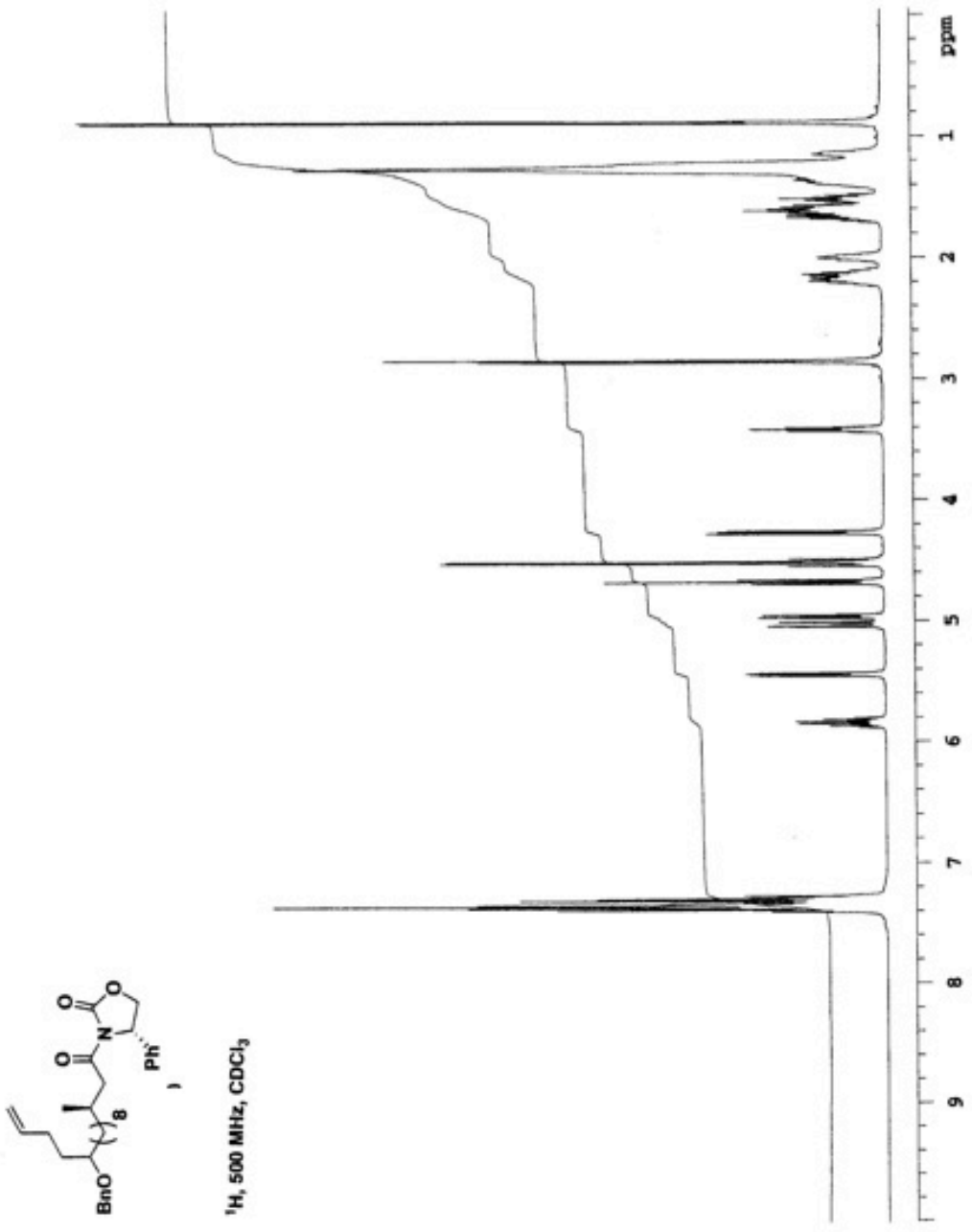

OBz
O
^{13}C, 125 MHz, $CDCl_3$
200
180
160
140
120
100
80
60
40
20
ppm

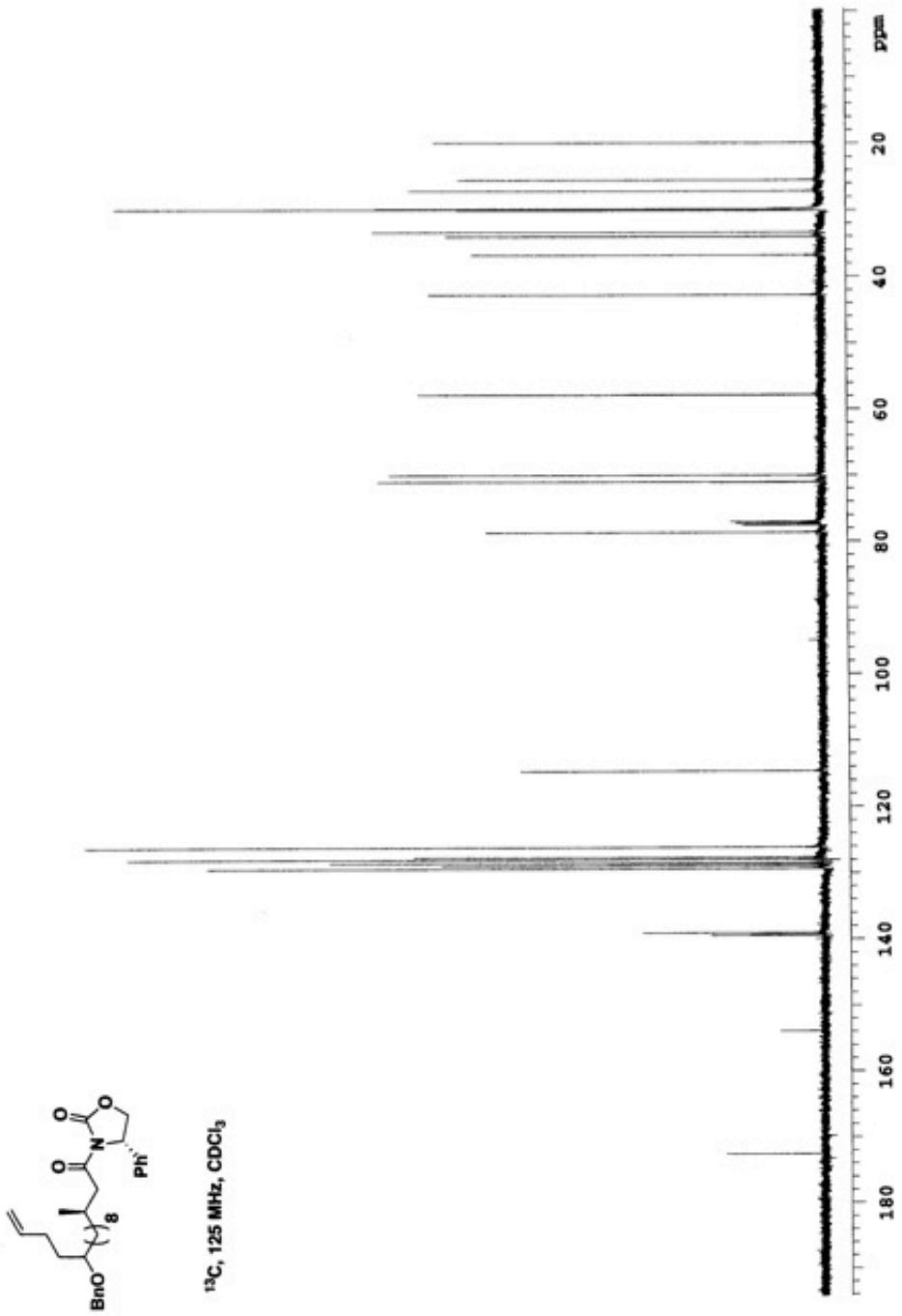

ppm
1
2
3
4
5
6
7
8
9
O
^{1}H, 500 MHz, $CDCl_3$

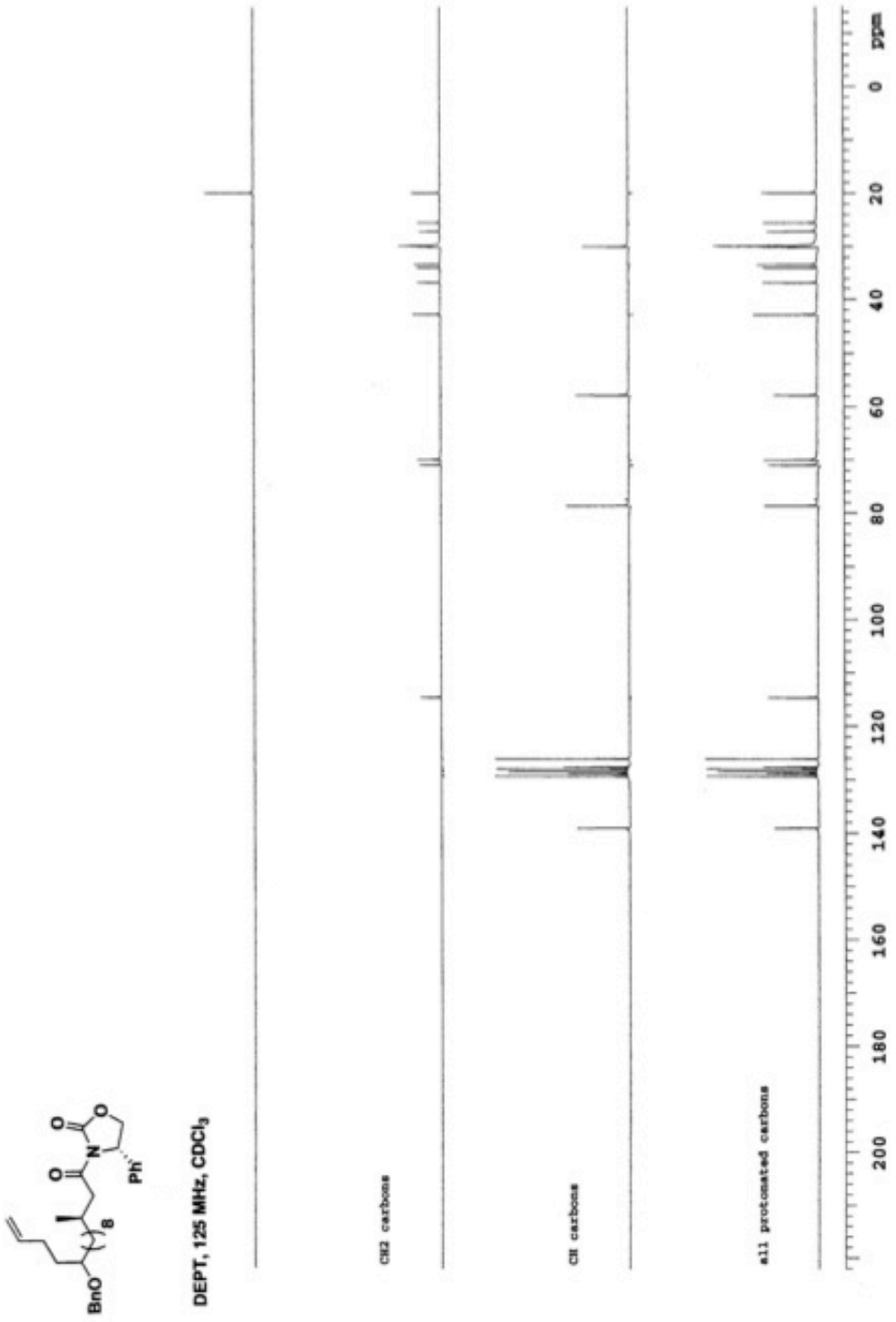

O
^{13}C, 125 MHz, $CDCl_3$
ppm
20
40
60
80
100
120
140
160
180

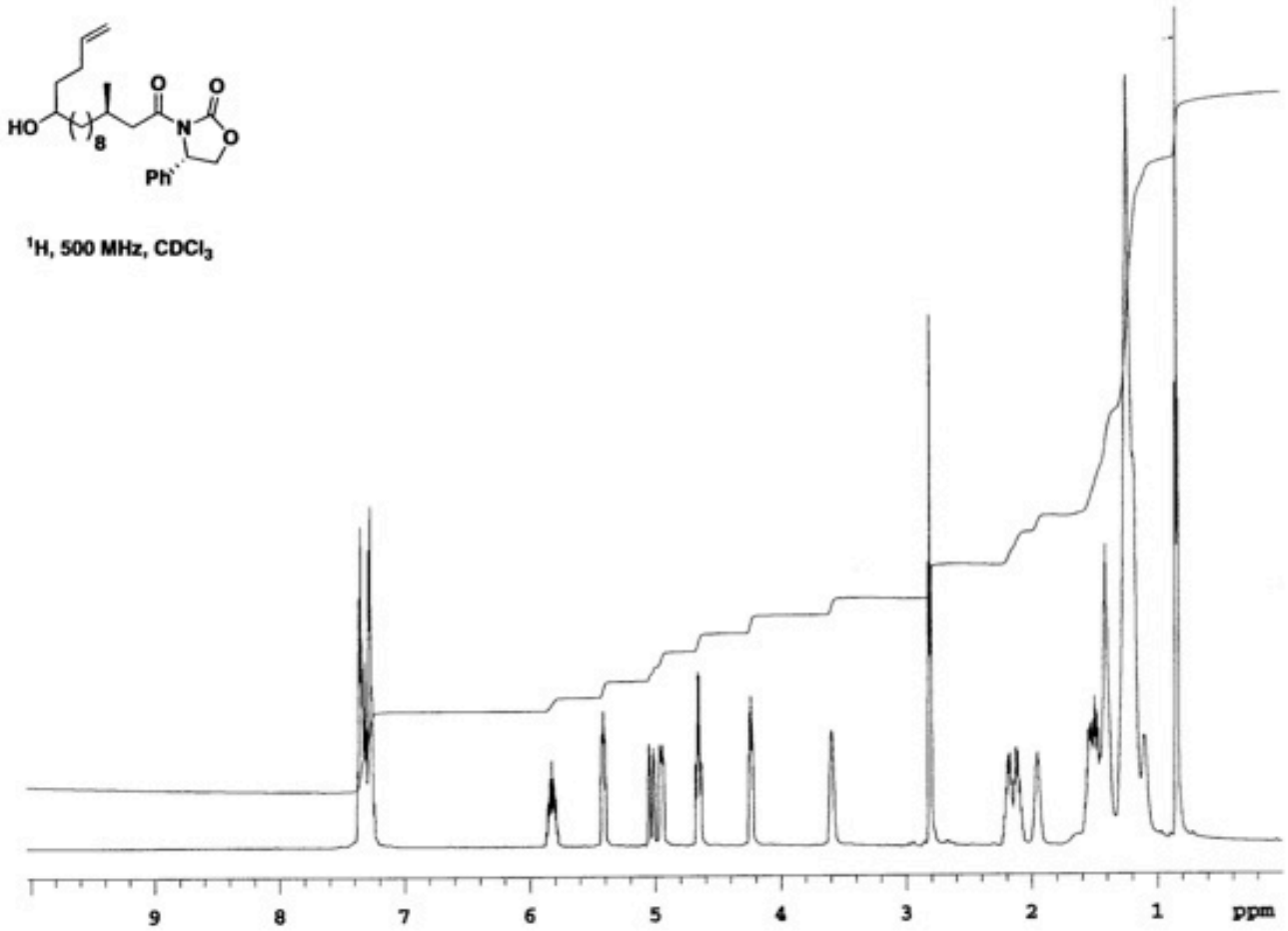

BnO
8
Ph
^{1}H, 500 MHz, CDCl$_3$
ppm
1
2
3
4
5
6
7
8
9


BnO
Ph
^{13}C, 125 MHz, $CDCl_3$
ppm
20
40
60
80
100
120
140
160
180

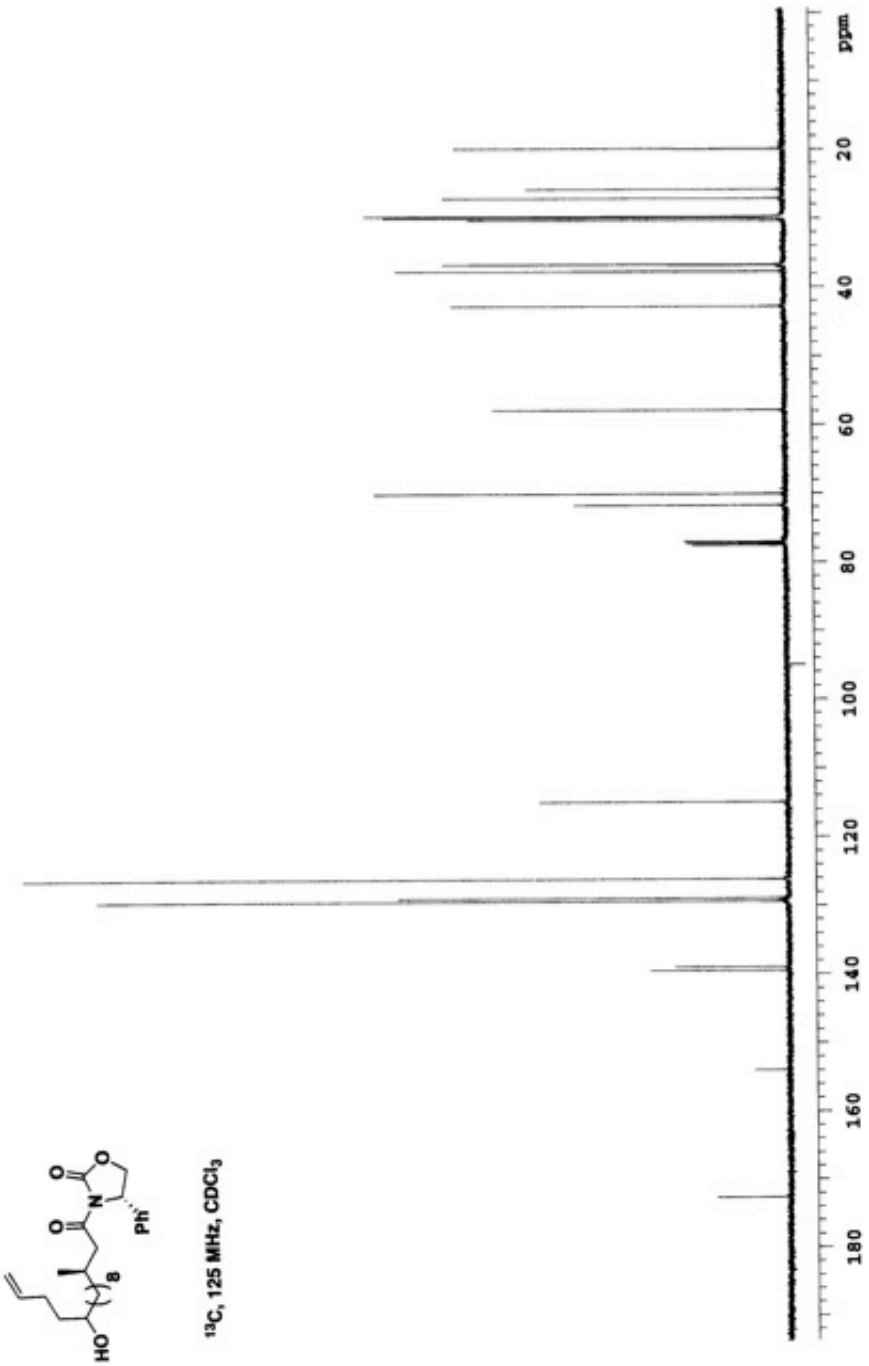

BnO
8
Ph
^{1}H, 500 MHz, CDCl$_3$
ppm

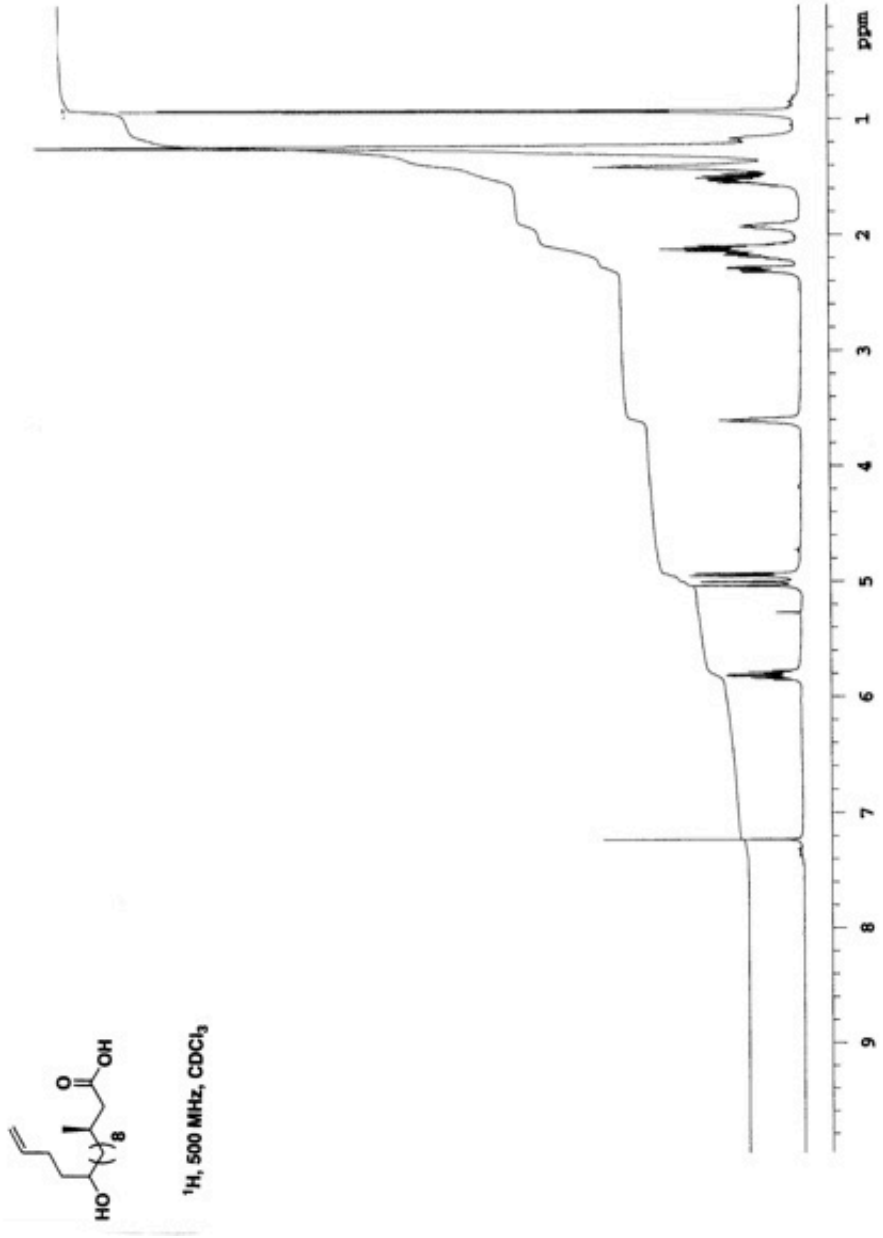

ppm
20
40
60
80
100
120
140
160
180
^{13}C, 125 MHz, $CDCl_3$
BnO
Ph

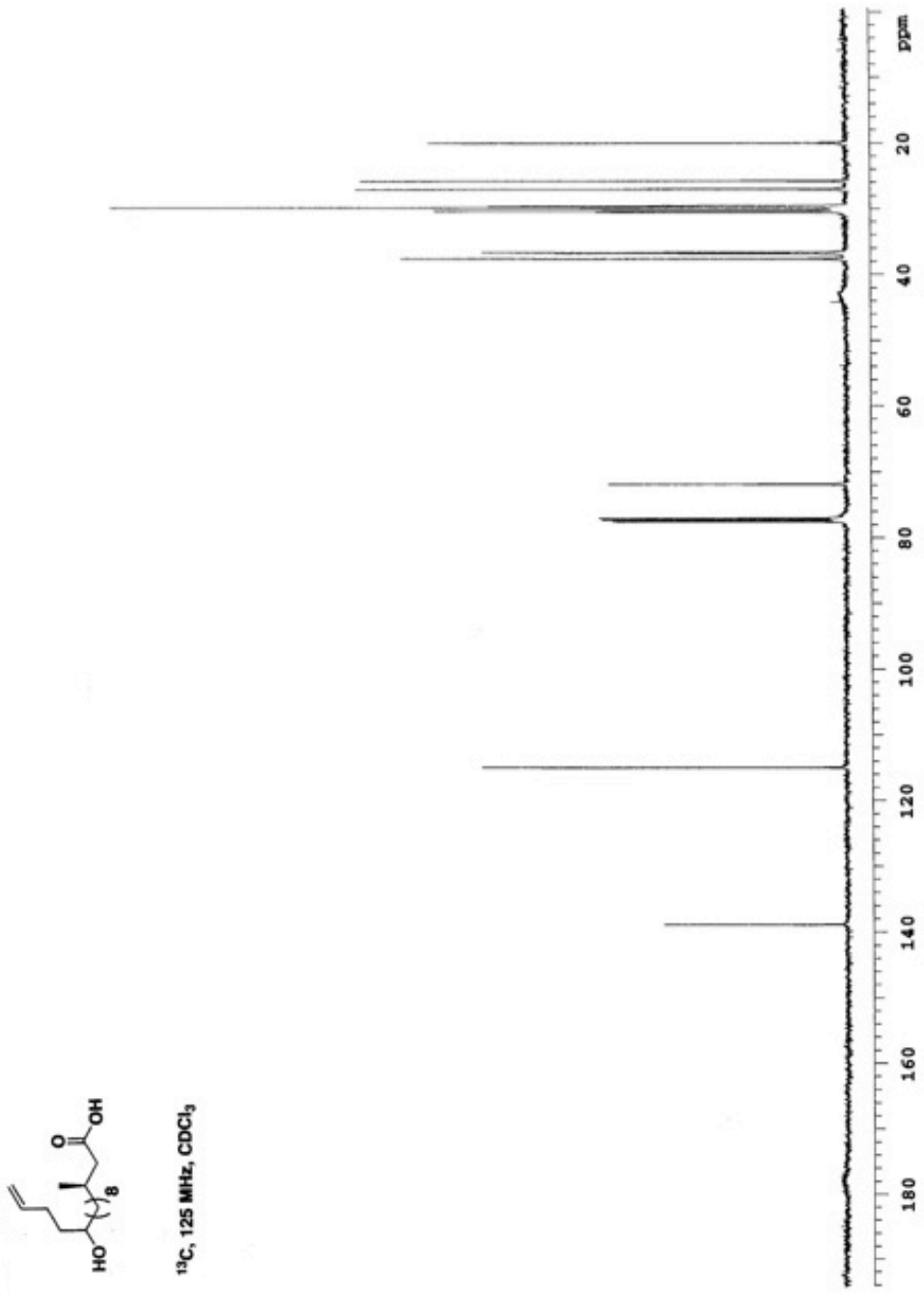

DEPT, 125 MHz, CDCl3
CH2 carbons
CH carbons
all protonated carbons
200
180
160
140
120
100
80
60
40
20
0
ppm
BnO
Ph
N
O
O
O
8

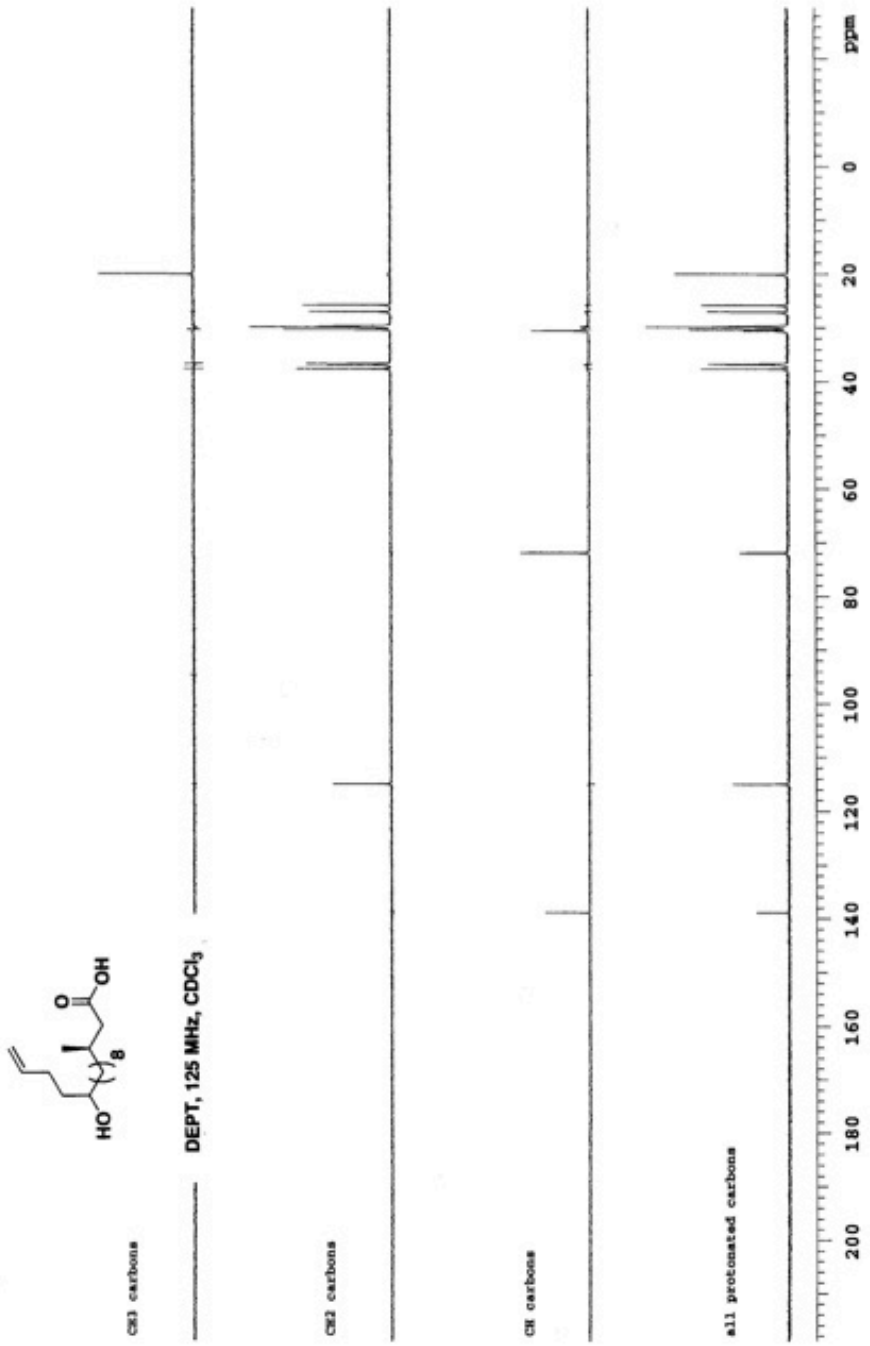


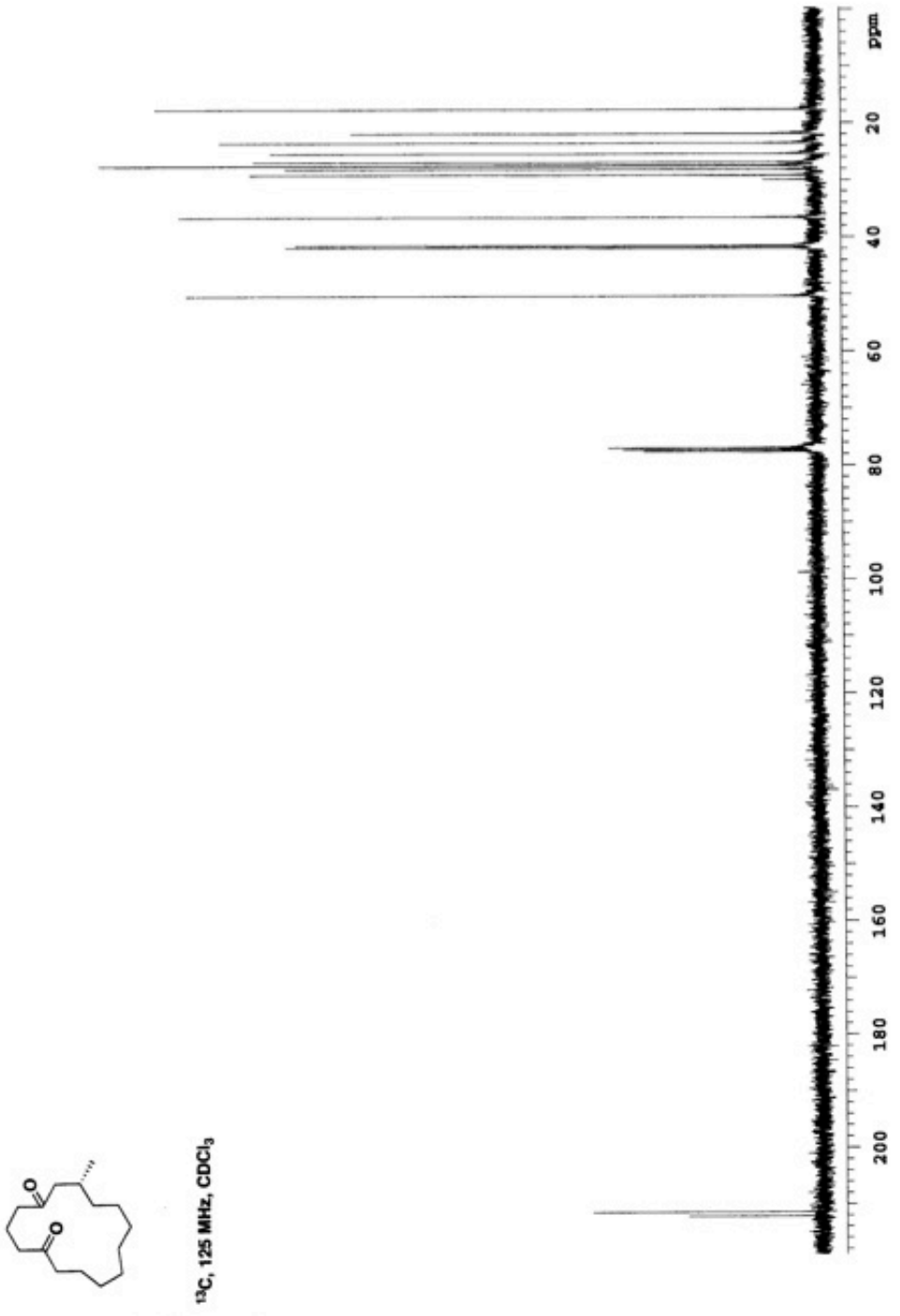
^{1}H, 500 MHz, $CDCl_3$

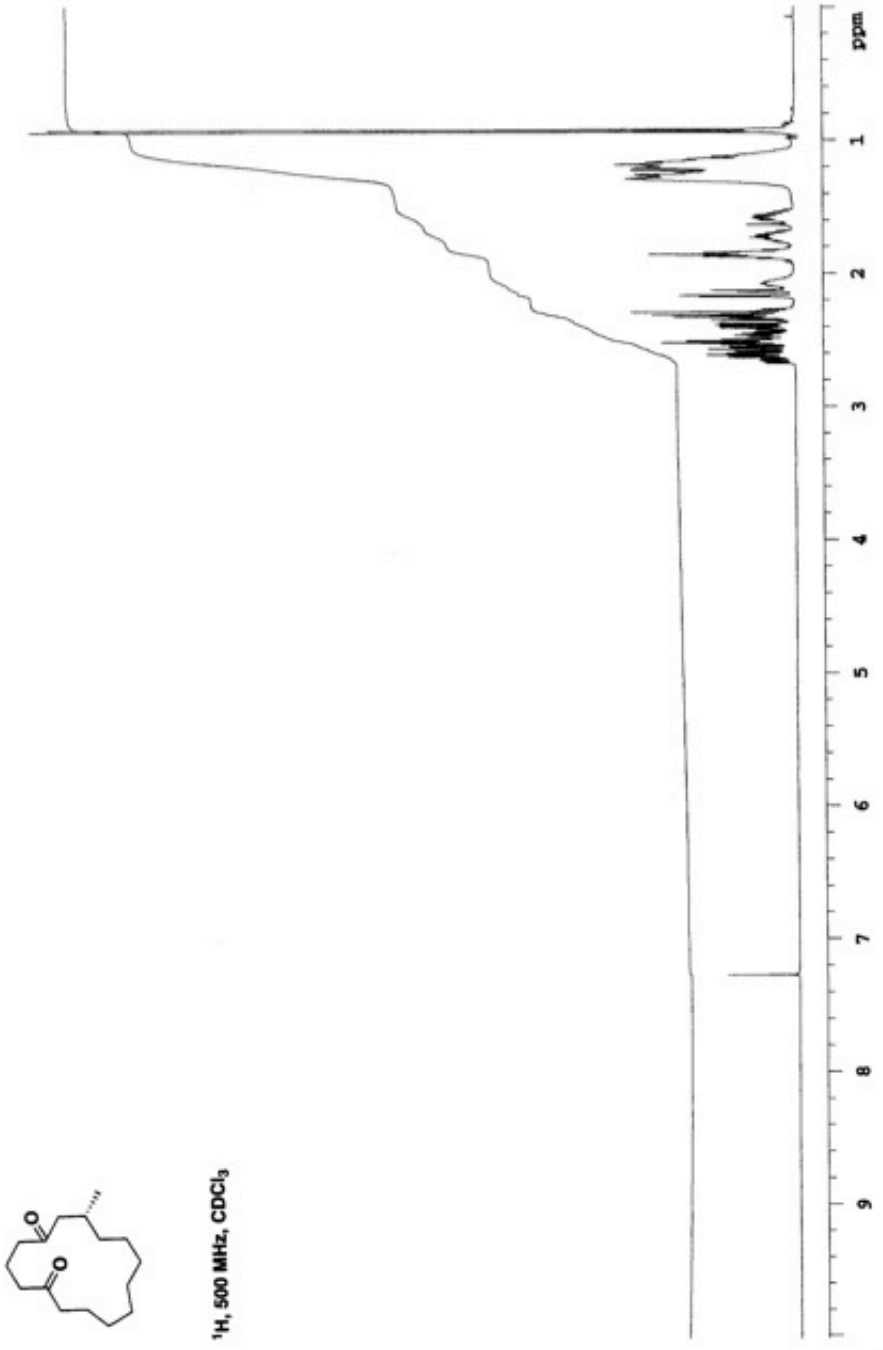

ppm
20
40
60
80
100
120
140
160
180
^{13}C, 125 MHz, $CDCl_3$
HO
8
Ph

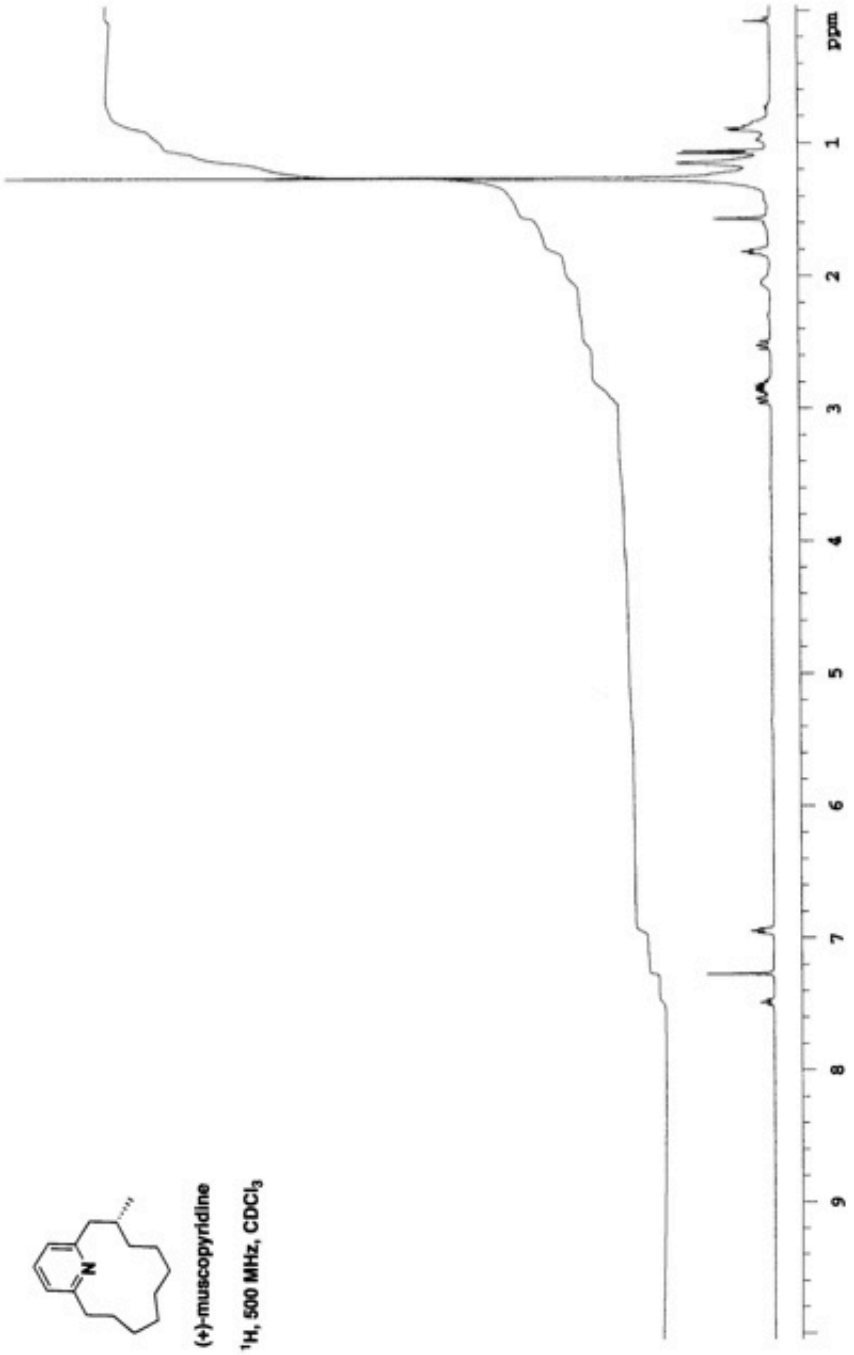

HO
O
OH
8
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9

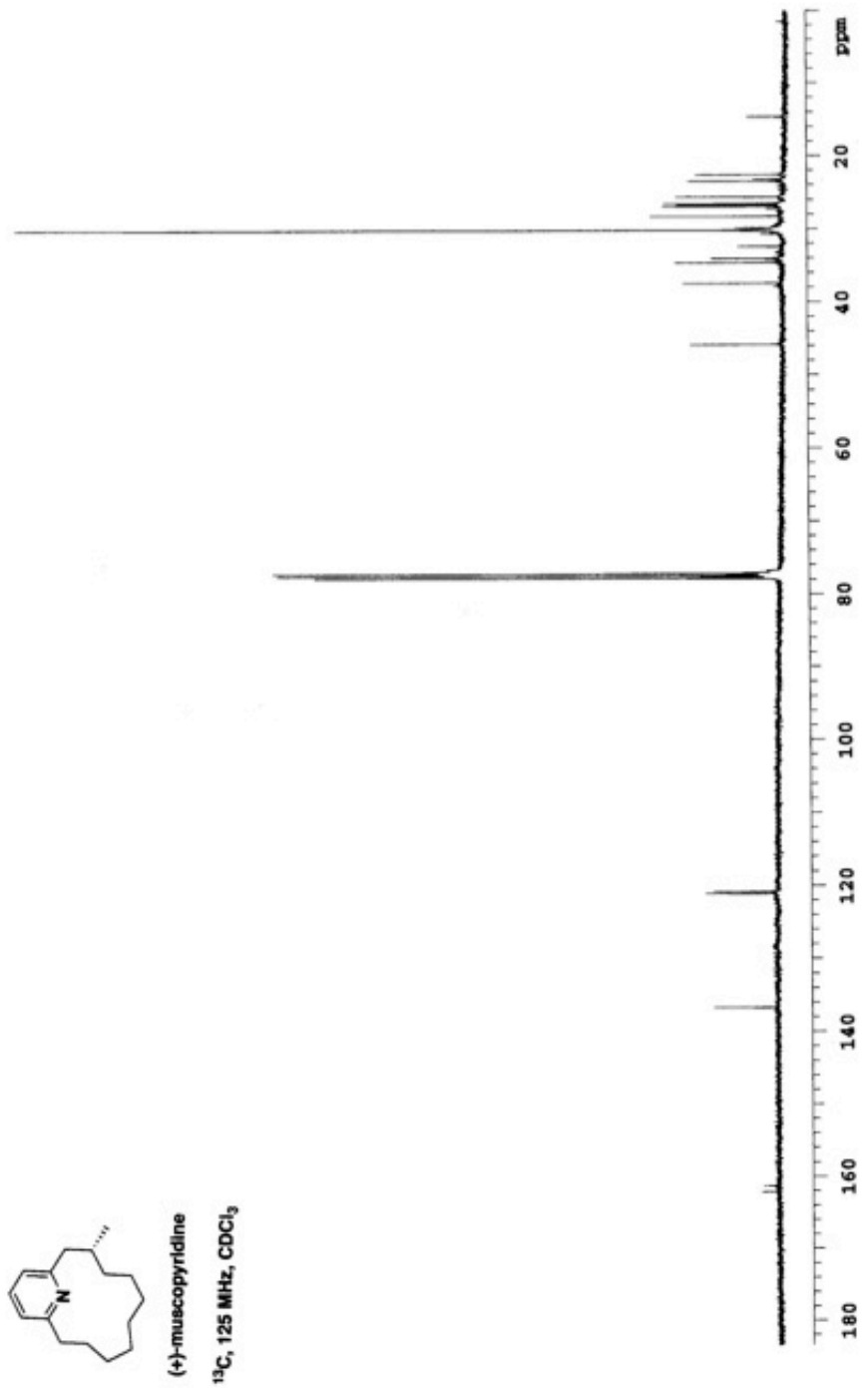

HO
O
OH
8
^{13}C, 125 MHz, CDCl$_3$
ppm
20
40
60
80
100
120
140
160
180

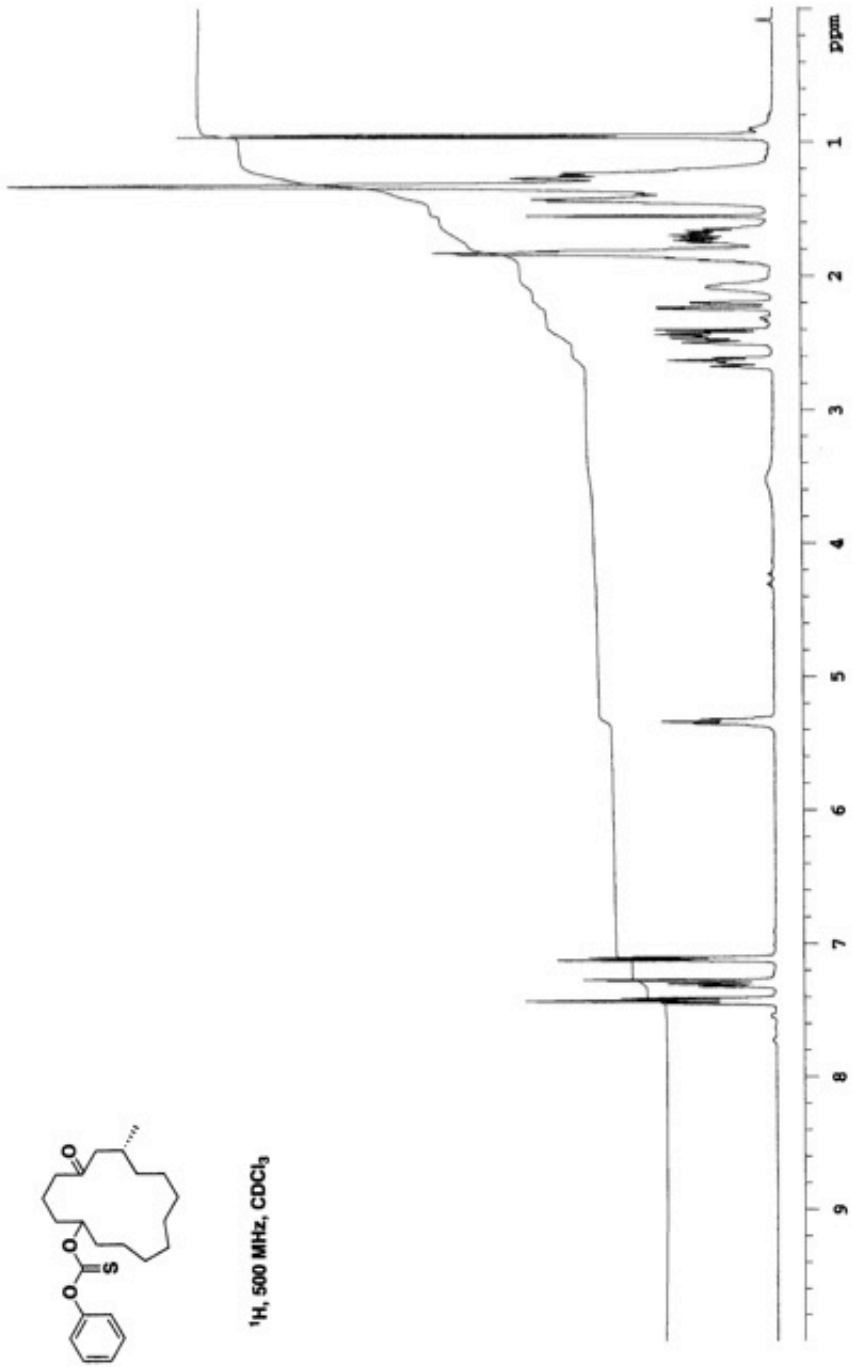

DEPT, 125 MHz, CDCl3
CH3 carbons
CH2 carbons
CH carbons
all protonated carbons
HO
OH
O
8
200
180
160
140
120
100
80
60
40
20
0
ppm

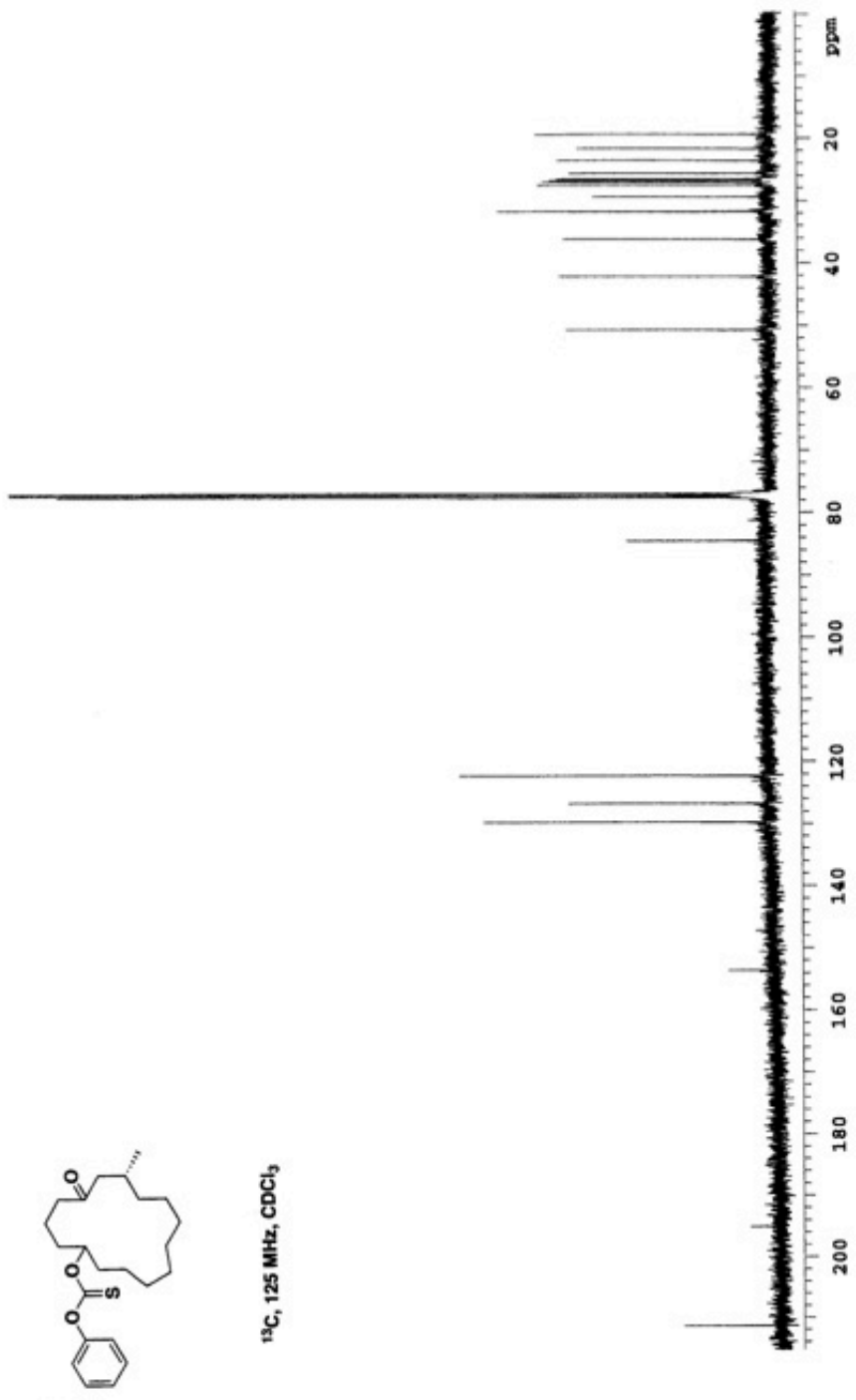

O
O
^{13}C, 125 MHz, $CDCl_3$
ppm
20
40
60
80
100
120
140
160
180
200

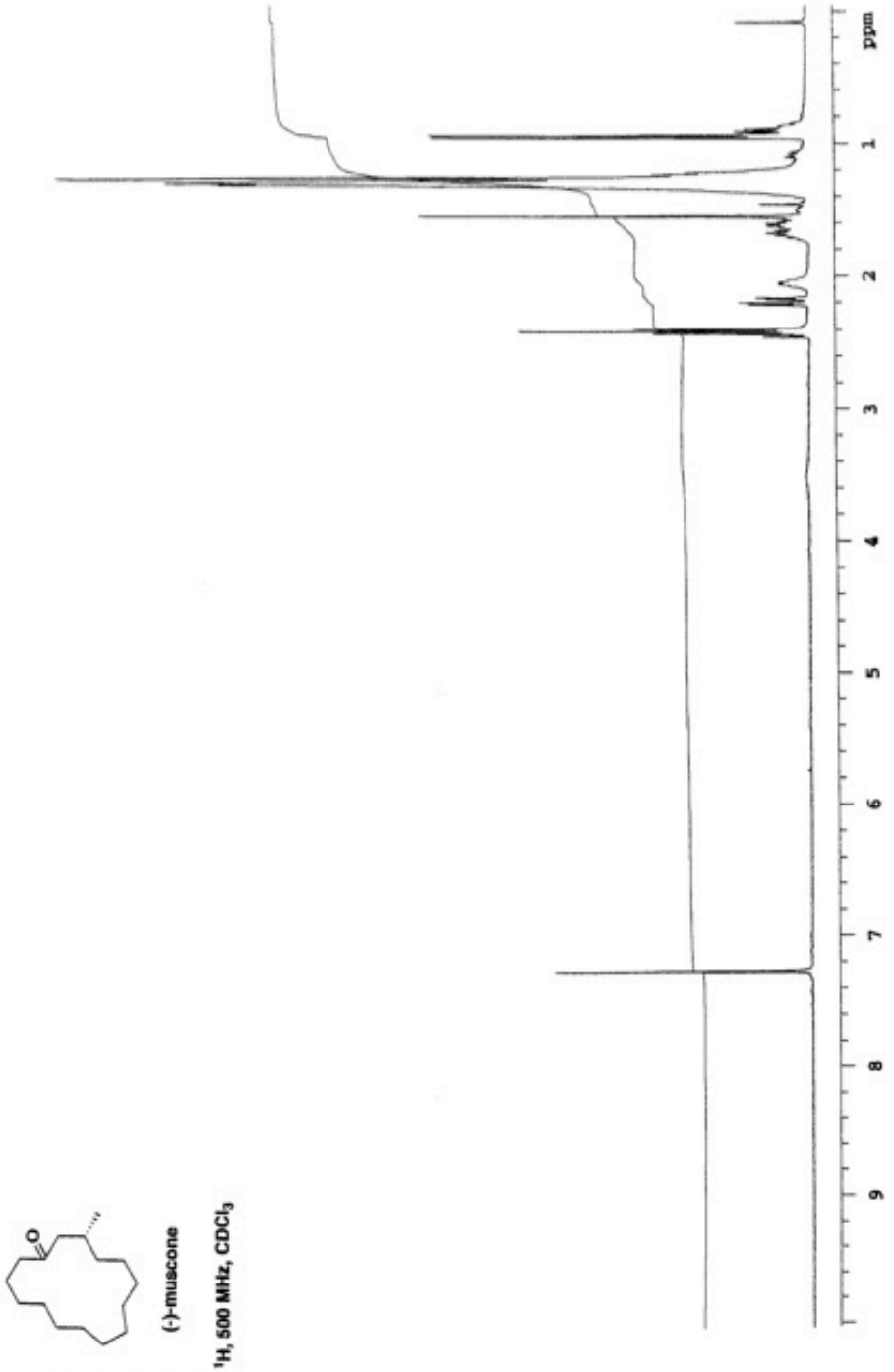

O
O
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9

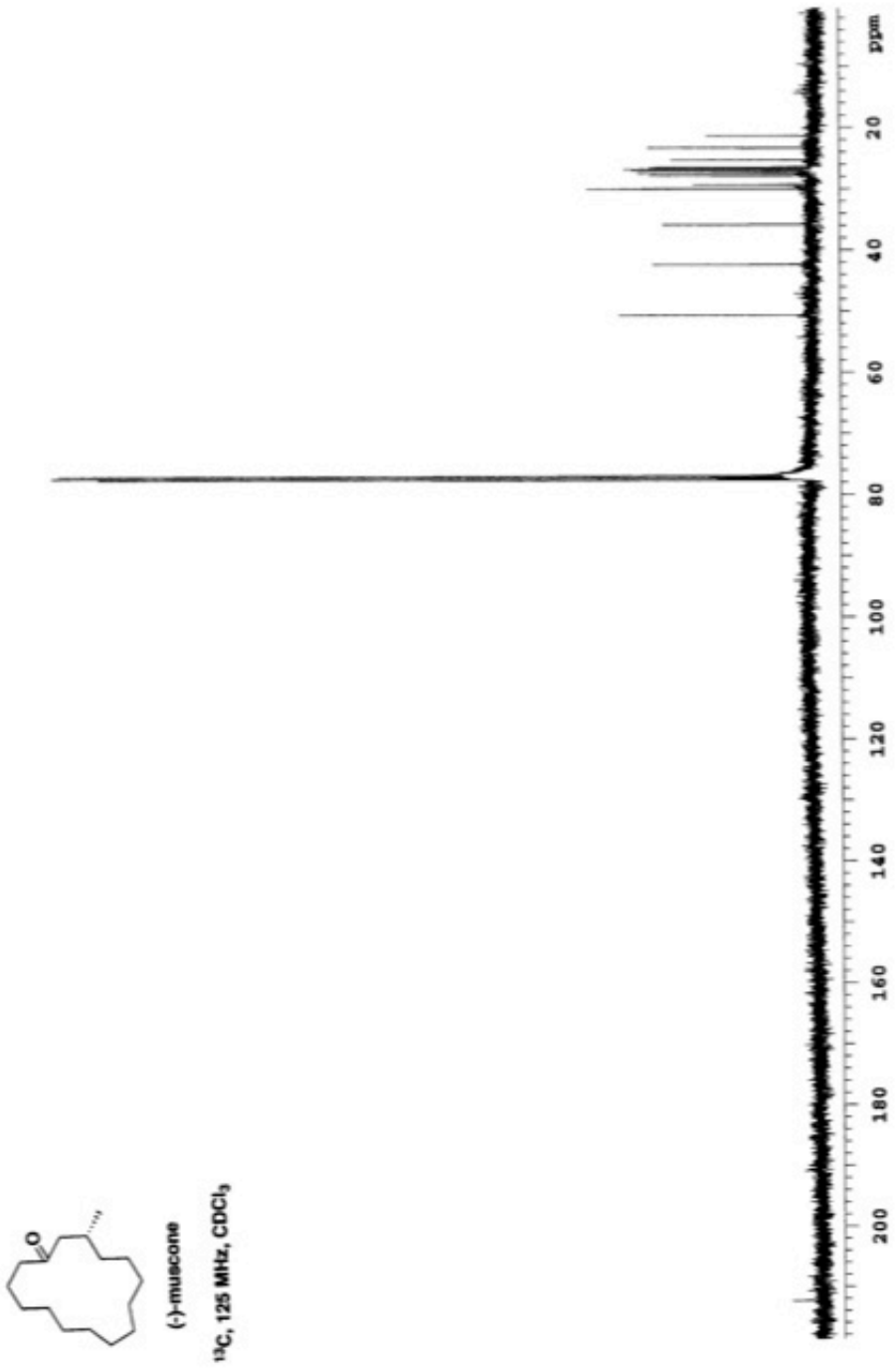

(+)-muscopyridine
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9


(+)-muscopyridine
^{13}C, 125 MHz, $CDCl_3$
180
160
140
120
100
80
60
40
20
ppm


ppm
1
2
3
4
5
6
7
8
9
O
O
O
S
^{1}H, 500 MHz, $CDCl_3$


O
O
O
S
O
^{13}C, 125 MHz, $CDCl_3$
200
180
160
140
120
100
80
60
40
20
ppm


O
(-)-muscone
^{1}H, 500 MHz, $CDCl_3$
ppm
1
2
3
4
5
6
7
8
9


(-)-muscone
^{13}C, 125 MHz, $CDCl_3$
200
180
160
140
120
100
80
60
40
20
ppm